Pediatrics

VOLUME 2 NOVEMBER 1948 NUMBER 5

TOXOPLASMOSIS IN CHILDREN

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THE first report of human toxoplasmosis was made less than 10 years ago by Wolf, Cowen, and Paige,[1] and we still have a great deal to learn about the clinical, epidemiologic, and laboratory features of this disease. Since the literature on toxoplasmosis has been well reviewed recently,[2] no attempt will be made to do so in this report. However, we would like to add five proven cases of toxoplasmosis, and eight cases in which there is strong evidence to support this diagnosis. The main purpose of this paper is to point out that only one or two of the cardinal manifestations may be present in a patient in whom the organism has been found and the diagnosis established. It is our impression that a patient may not have either characteristic cerebral calcification or chorioretinitis and still have clinical toxoplasmosis. The specificity of the neutralization test has to be seriously questioned in the light of recent findings. A report is now being prepared of the results of these studies.

CLINICAL MANIFESTATIONS OF TOXOPLASMOSIS

In man, toxoplasmosis can be either congenital or acquired. The most common signs in the congenital form of the disease are hydrocephalus, chorioretinitis, cerebral calcification, and convulsions. Primary optic atrophy and a searching nystagmus also have been frequently observed. Sabin[3] has suggested that anencephalus also might be caused by toxoplasmosis. The congenital form of the disease is usually fatal, but in some patients a chronic stage is reached and they may live for years. Congenital visceral manifestations also occur, the primary complaints being cyanosis and dyspnea with hepatomegaly and splenomegaly;[4] in one reported instance this occurred in identical twins both of whom also had obstructive jaundice for several months.[5]

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(Received for publication June 24, 1948.)

The acquired form of toxoplasmosis usually produces the symptoms of an acute encephalitis[6] which may be fatal; or, more rarely, it produces the symptoms of an atypical pneumonia with a generalized maculopapular skin eruption resembling Rocky Mountain Spotted Fever.[7] One adult with symptoms of fever, diarrhea, crampy abdominal pain and pain in the elbow was found from a muscle biopsy to harbor Toxoplasma.[8] Whether or not the Toxoplasma were the cause of the patient's symptoms was not proven, but the patient eventually recovered. There is also a latent form of the disease which occurs both in children and adults.[3,9,10] Callahan has shown that 2% of the people in a random sample in the St. Louis area have a positive neutralization test against Toxoplasma.[9]

On the basis of known information, the clinical manifestations of human toxoplasmosis can be classified as follows:

I. Congenital Toxoplasmosis
  A. Acute and chronic cases with neurologic signs and symptoms.
    1. Encephalomyelitis.
    2. Hydrocephalus.
    3. Convulsions.
    4. Chorioretinitis.
    5. Cerebral calcifications.
    6. Microcephalus.
    7. Anencephalus.
    8. Microphthalmus.
  B. Acute cases with visceral signs and symptoms.
    1. Pneumonitis.
    2. Myocarditis.
    3. Hepatomegaly.
    4. Splenomegaly.
    5. Jaundice.
  C. Latent cases.
II. Acquired Toxoplasmosis.
  A. Acute cases with neurologic symptoms.
    1. Encephalitis.
  B. Acute cases with visceral signs and symptoms.
    1. Pneumonitis.
    2. Exanthemata.
    3. Enteritis.
  C. Latent cases.

In 1944, we recognized our first clinical case of toxoplasmosis at the University of Minnesota Hospitals.[10] Since that time 13 additional cases have been seen which we believe may have had the disease. In five of the patients, organisms resembling Toxoplasma were seen microscopically, but in three of these patients not all of the characteristic tetrad of symptoms and signs were present (i.e. hydrocephalus, chorioretinitis, cerebral calcifications, convulsions). One additional patient manifested the tetrad but the organism was not isolated. Four patients manifested three of the tetrad, and three appeared to have an acquired type of toxoplasmic encephalitis.

Case Reports

Case 1. This was a stillborn male delivered at St. Joseph's Hospital, St. Paul, Minnesota. The mother's pregnancy history was supposedly normal. The postmortem examination done at the University of Minnesota Medical School revealed a normal appearing baby and viscera. The brain was small but there was an extreme internal hydrocephalus; the cortex was only a thin membrane. The basal ganglia contained a white chalky substance; the aqueduct was nearly occluded; and chalky material floated in the ventricular fluid. Microscopically, numerous areas of granulomas, calcification, and Toxoplasma both singularly and in pseudocysts were scattered throughout the brain. No attempt was made to isolate the Toxoplasma from this patient.

Case 2. This stillborn male infant was delivered at the University Hospitals after a craniocleisis had been performed because of a massive hydrocephalus. The mother was a 16-year-old unmarried female whose pregnancy was normal except that she had a generalized maculopapular skin eruption during the eighth month that lasted three weeks. The mother was admitted to the hospital because of the abnormal size of her uterus. Roentgenograms done at this time showed that the fetus had an enlarged head, but no calcification could be seen. Pieces of the brain saved at the time of the craniocleisis were inoculated into mice and guinea pigs with negative results. Histologic sections of the brain revealed scattered areas of granulomas, calcification, and an occasional organism resembling Toxoplasma. Blood taken from the mother postpartum gave a positive neutralization for toxoplasmosis.

Case 3. This two-week-old Japanese female was admitted to the hospital because she failed to eat well and was losing weight. She had also had some fever and diarrhea previous to admission. Physical examination was negative except for some vitreous opacities in the left eye. Examination of the blood showed a leukocytosis with an eosinophilia of 25%. Gradually the patient became lethargic, and developed tremors and fever. The spinal fluid was xanthochromic and had 72 cells and 166 mg./1100 cc. fluid protein. X-rays of the skull revealed calcification over the sphenoid, temporal, and posterior parietal areas. An encephalogram showed small pockets of air over the surface of the brain as well as in the ventricles. In spite of sedatives and general supportive therapy, the patient's symptoms persisted and she expired at six weeks of age. On postmortem examination multiple cystic and necrotic areas with calcium deposition were distributed throughout the brain and cord. Microscopically Toxoplasma were seen singly and in pseudocysts both with and without areas of granulomas and calcification. Sera from the patient, mother and father showed no neutralization for toxoplasmosis; however, the specimens were kept at room temperature for several days by error so the tests were not reliable.[33]

Case 4. This four-month-old male was admitted to the hospital because of progressive hydrocephalus since birth. The mother's pregnancy was complicated by pre-eclampsia so it was terminated at eight months' gestation. The premature baby did well except for the hydrocephalus and several cyanotic episodes during the third week of life. Physical and laboratory examination revealed only the hydrocephalus and a xanthochromia with a pleocytosis of the spinal fluid. Encephalograms revealed markedly dilated lateral ventricles with only 1 cm. of cortex remaining. Sera from the patient, the mother, the father and one sibling all neutralized Toxoplasma. Since favorable results had been obtained in a previous case of hydrocephalus by cauterization[10] of the choroid plexus, a similar procedure was performed in this patient. Following this procedure, the hydrocephalus seemed to be relieved but one month later he was discovered to have a Wilm's tumor of the right kidney from which he expired two months later. Postmortem examination confirmed the clinical diagnosis of a Wilm's tumor and revealed several areas of metastasis in the brain. Organisms resembling Toxoplasma were found only in the intestine and mesentery.

Case 5. This three-week-old female infant was also admitted to the hospital because of a progressive hydrocephalus since birth, and a mild diarrhea. Delivery was so difficult that the infant's skull was fractured; however, exploration for subdural hematoma revealed only a slight thickening of the dura. This was obviously not the primary cause of the hydrocephalus. Ventriculograms revealed a marked internal hydrocephalus with a cortex less than 1 cm. in thickness. An attempt at cauterization of the choroid plexus was not made because of a marked ventriculitis; however, a biopsy of the choroid plexus revealed organisms resembling Toxoplasma. Sera from the patient and her mother were likewise positive for toxoplasmic neutralization. The patient lived until 18 months of age; when she expired her head circumference was 190 cm.

Case 6. This 5½-month-old female was admitted because of a progressive hydrocephalus since birth, and convulsions and retardation of motor development since 3½ months of age. Calcification of the brain was seen on X-ray and chorioretinitis with bilateral optic atrophy and vitreous clouding was seen ophthalmoscopically. The hydrocephalus was probably of the obstructive type so a ventriculostomy was done but without effect. At 18 months of age the hydrocephalus had progressed to a head circumference of 56 cm., and the baby was functioning at a two month age level. The toxoplasmic neutralization test was positive for both the mother and the patient. The complement fixation test for toxoplasmosis was also positive for the patient's serum.

Case 7. This three-week-old female was admitted to the hospital with a history of twitchings, failure to eat well, and failure to gain weight since birth. Several members of the family were institutionalized with feeblemindedness and twitchings. Pneumoencephalogram revealed marked atrophy and internal hydrocephalus. The baby developed also a progressive hydrocephalus which responded to cauterization of the choroid plexus but did not affect the delayed motor development. When last seen at 14 months of age, she was blind, had bilateral optic atrophy, and would not sit up or hold up her head. Sera from the patient showed positive neutralization for toxoplasmosis at one month, 1½ months and 3½ months of age but negative neutralization at nine months and 13 months of age. The mother's serum also gave a positive neutralization test.

Case 8. This one-year-old female child had a history of a searching gaze since birth, convulsions, failure to hold her head up until six months of age, and failure to sit up. Examination revealed a microcephalus, bilateral optic atrophy, and chorioretinitis of the left eye. Pneumoencephalogram revealed diffuse large subarachnoid accumulations of air compatible with atrophy and cyst formation. Neutralization tests on this patient and her mother were unreliable, as the sera were kept at room temperature for several days by error.

Case 9. This 17-month-old female was first seen by a doctor at three months of age for poor eyesight and poor coordination. At five months of age, retinal and vitreous pathology was discovered. The child was definitely retarded in her motor and mental development. Physical examination revealed microcephalus, nystagmus, and a bilateral chorioretinitis and coloboma on the right side. Skull X-rays and a pneumoencephalogram revealed extensive small irregular calcifications throughout the brain and brain atrophy with an internal hydrocephalus. The patient's mother had vitreous floaters one month before her delivery and also developed a central chorioretinitis immediately following her delivery. She had also been bitten by rabbits and fleas during the fourth month of her pregnancy following which she developed a "chest cold." Neutralization tests on this patient and her mother were likewise unreliable as the sera were kept at room temperature for several days by error.

Case 10. This case was reported in detail previously by one of us.[10]

Case 11. This male infant was first seen by us at two months of age because of diarrhea and a progressive jaundice since birth. Liver function tests revealed an obstructive type of jaundice.* He gradually recovered from the jaundice but he was readmitted to the hospital at 6½ months of age because of convulsions. All tests were negative except for a pneumoencephalogram which showed brain atrophy and internal hydrocephalus. His sera neutralized Toxoplasma in the rabbit and it also fixed complement at a titer of 1:512. Six months later his sera still neutralized Toxoplasma in the rabbit but the complement fixing titer dropped to 1:128. Sera from the mother and father likewise neutralized Toxoplasma in the rabbit and fixed complement. When seen at 2½ years of age, he was blind and greatly retarded in his motor and mental development. Examination revealed a microcephalus and a bilateral optic atrophy with chorioretinitis and vitreous floaters. A toxoplasmic skin test antigen† which was applied intradermally on the arm of the patient, his mother, and his father produced erythema and swelling from 2 to 5 cm. in diameter in 24 to 48 hours. These were interpreted as positive reactions.

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* We have tested the serum from another patient and her mother seen by Dr. S. L. Arey of Minneapolis with similar signs and symptoms of obstructive jaundice since birth, microcephaly, chorioretinitis, cerebral calcification, hepatomegaly, and splenomegaly. Both the mother's and baby's sera showed marked neutralization of Toxoplasma in the rabbit.

† The toxoplasmic skin test antigen was kindly furnished by Dr. J. K. Frenkel of the University of California Medical School, San Francisco.

Case 12. This 2½-year-old male was admitted to the hospital with a history of listlessness, fever, anorexia, and irritability of two months' duration. Physical examination revealed positive meningeal signs, a cracked-pot resonance to percussion of the skull, and a three diopter elevation of the optic discs bilaterally. Ventriculograms revealed a questionable internal hydrocephalus and the ventricular fluid revealed a pleocytosis, most of which were lymphocytes. The patient's symptoms and physical findings gradually disappeared on supportive therapy and when seen five months later he was completely normal. The neutralization test for toxoplasmosis was positive on this patient's serum at the time of the disease, but became negative seven months later.

Case 13. This 14-year-old male had a history of fever, sore throat, coryza and chest pain followed by neck stiffness, headaches, diplopia, nausea, vomiting, and muscular twitchings for two months prior to admission to our hospital. Physical examination revealed paresis of the right lateral rectus, and numerous bilaterally enlarged cervical lymph nodes. Spinal fluid examination revealed 180 mononuclear cells, and a positive Pandy reaction; the cultures of the fluid were sterile on several occasions. Neutralization and complement fixation tests for toxoplasmosis were positive at the time of the disease but were both negative one year later. Toxoplasmic skin test antigen applied one year later likewise produced no reaction. While in the hospital, he had transitory stiffness of the neck and weakness of the right arm and shoulder. He was treated empirically with penicillin and sulfadiazine for four weeks, during which time he recovered completely.

Case 14. This 12-year-old male was admitted to the hospital with a history of progessive lethargy, fever, photophobia, diplopia and ataxia following a football injury. Physical examination revealed bilateral papilledema, a dilated right pupil, and a paresis of the right VII and XII cranial nerves. Trephine holes in the skull were made for a subdural hematoma and the cerebellum was likewise explored but nothing was found. Dye injected intraventricularly could not be recovered from the cisterna magna and a ventriculogram revealed dilated lateral ventricles. A tube was inserted into the right lateral ventricle and drained into the cisterna magna in order to relieve the pressure. After several weeks the tube was removed, and the patient recovered completely. Serum from the patient showed positive neutralization and positive complement fixation for toxoplasmosis. Sera from his brother and father likewise gave a positive neutralization test.

Comment

The significant data from the 14 patients studied by us are presented in Table I. It immediately becomes obvious that most of the patients had the onset of their illness in utero, at birth, or shortly after birth. In Case 10 (previously reported[10]) the infection probably remained latent for a period of time and then produced chronic symptoms. At the present time, nine of the patients are still alive and, except for one or two of them, the chances of their living for many years are very good. It, therefore, seems likely that if a patient can survive the acute infection, a chronic state can be reached that is compatible with life. Because of the nature of their illness and the similarity to Sabin's case,[6] we believe that Cases 12, 13, and 14 had acquired toxoplasmic encephalitis. All of them are alive and well at the present time.

Convulsions were present in only three of the patients in marked contrast to the incidence previously reported.[11,12] Muscle tremors or twitchings were present in three additional patients, however. All of our patients with the congenital form of the disease had a hydrocephalus. Four of these had a normal head size and three had a microcephalus in spite of the internal hydrocephalus. Mental deficiency was present in six of the patients but Case 10 had a better than average intelligence in the presence of a marked hydrocephalus. None of the three patients with acquired encephalitis seemed to have any impairment of their intelligence as a result of the infection.

Chorioretinitis was observed in five patients, but in the three proven cases that lived none had chorioretinitis. This decreased incidence of chorioretinitis is again in contrast

TABLE I

Analysis of Cases

	Proven Cases					Probable Cases								
						Tetrad	Three of tetrad					Acquired encephalitis		
	1	2	3	4	5	6	7	8	9	10	11	12	13	14
Anamnestic data														
Sex	M	M	F	M	F	F	F	F	F	F	M	M	M	M
Age at Onset	fetal	fetal	birth	1 mo.	fetal	fetal	birth	birth	birth	?	birth	2½ yr.	14 yr.	12 yr
Duration of Illness	...	...	6 wk.	5 mo.	3 mo.	7 mo.	2 yr.	2 yr.	2 yr.	11 yr.	2½ yr.	2 mo.	2 mo.	2 wk.
Age at Death	still born	birth	6 wk.	6 mo.	1½ yr.	alive	alive	alive	alive	alive	alive	alive	alive	alive
Symptoms and signs														
Neurologic														
Convulsions	...	...	–	–	–	+	–	+	–	–	+	–	–	–
Muscle twitchings	...	...	+	–	–	–	+	–	–	–	+	–	+	–
Internal hydrocephalus	+	+	+	+	+	+	+	+	+	+	+	?	...	+
Microphalus	–	–	–	–	–	–	–	+	+	–	+	–	–	–
Mental deficiency	...	...	...	+	..	+	+	+	+	–	+	–	–	–
Ocular														
Chorioretinitis	...	...	–	–	–	+	–	+	+	+	+	–	–	–
Microphthalmos	...	...	–	–	–	...	–	+	+	–	+	–	–	–
Strabismus or nystagmus	...	...	...	+	–	...	+	+	+	–	+	–	+	+
Other symptoms and signs														
Jaundice	–	...	–	+	–	–	–	–	–	–	+	–	–	–
Splenomegaly	–	...	–	–	–	–	–	–	–	–	+	–	–	–
Hepatomegaly	–	...	–	–	–	–	–	–	–	–	+	–	–	–
Maculopapular rash	–	...	–	–	–	–	+	–	–	–	–	–	–	–
Feeding difficulty	...	...	+	+	–	–	+	–	+	–	–	–	–	–
Diarrhea or vomiting	...	...	+	+	+	–	+	–	–	–	+	–	–	–
Pulmonary signs	...	...	–	+	–	–	–	–	–	–	–	–	+	–
Lymphadenopathy	...	...	–	–	+	–	–	–	–	–	–	–	+	–
Fever	...	...	+	–	–	...	–	–	–	–	–	+	+	+
Subnormal or labile body temperature	...	...	+	–	–	–	–	–	–	–	–	–	–	–
Calcification in brain at autopsy or x-ray	+	+	+	–	–	+	+	–	+	+	–	–	–	–
Laboratory data														
Cerebrospinal fluid														
High protein	...	...	+	+	+	–	+	–	–	...	–	–	–	–
Xanthochromia	...	...	+	+	–	–	–	–	–	...	–	–	–	–
Pleocytosis	...	...	+	+	+	–	–	–	–	...	–	+	+	–
Blood														
Anemia	...	...	–	+	–	–	+	–	–	–	+	–	–	–
Leukopenia	...	...	–	–	–	–	–	–	–	–	–	–	–	–
Leukocytosis	...	...	+	–	–	–	–	–	–	–	+	–	–	–
Eosinophilia	...	..	+	–	–	–	–	–	–	–	–	–	–	–
Wassermann or Kahn	...	...	–	–	–	–	–	...	...	–	–	–	–	–
Neutralization test														
Patient	...	...	–	+	+	+	+	–	–	+	+	+	+	+
Patient's mother	...	+	–	+	+	+	+	–	–	+	+	+	...	–
Patient's father	...	...	–	+	–	–	–	–	–	–	+	+	...	+
Other members of family	...	...	...	+	–	...	...	...	...	+	–	...	...	–
Complement fixation test	...	...	...	...	–	+	...	...	...	+	+	...	+	+
Autopsy														
Characteristic lesions containing Toxoplasma	+	+*	+	+	+*	...	...	...	...	...	...	...	...	...

+ indicates positive findings.
– indicates negative findings.
... indicates data not available (or not pertinent).
* biopsy.

to the previously reported incidence.[11,12] In Case 9, the mother also developed chorioretinitis with vitreous floaters during the last trimester of her pregnancy.

Feeding problems were present in four of the infants. In two of these, it was the presenting complaint to the doctor. One of these patients also had a very labile body temperature. Jaundice with hepatomegaly and splenomegaly was the presenting complaint in one of the infants seen by us and in another whose serum we tested and found positive for neutralizing antibodies.

Calcification of the brain was present in seven of the 14 cases. However, in several it was so minimal that it could have easily been overlooked if the diagnosis of toxoplasmosis had not been suspected.

The spinal fluid examination showed a pleocytosis and/or a xanthochromia in only four of the congenital cases and in all three of the acquired encephalitic cases. The blood counts did not appear significantly altered except for an occasional slight eosinophilia.[8]

The neutralization test for toxoplasmosis was found positive in all but three of the patients tested. In these three, the test might have been positive had the sera not remained at room temperature for several days, as Sabin and Ruchman have shown that the antibody is heat labile and is readily destroyed at room temperature.[13] The complement fixation test was positive in five of six patients tested. One patient's serum #11 showed a significant change in complement fixation antibody titer on a specimen that was obtained six months later. This furnishes further evidence that Toxoplasma might have been the cause of this patient's illness, as the complement fixation titer correlates closely with the acute disease in the experimental animal.[15] At the height of the illness of patient #13, his serum showed good neutralization of Toxoplasma and it fixed complement slightly; however, one year later both were negative as was his skin test with toxoplasmic antigen. Patient #11 had a marked reaction to toxoplasmic skin test antigen when it was injected intradermally.

Difficulty was experienced in isolating the toxoplasmic organism from the body fluids. Many injections of blood and spinal fluid from several of the patients were made into both guinea pigs and mice intracerebrally and intraperitoneally without positive results. This has likewise been the experience of other workers. Failure to isolate the organism in at least several of the cases might have been because the disease was in a chronic state and few if any live Toxoplasma were present in the body. In the patients with acquired encephalitis, the spinal fluid was inoculated only into ordinary bacteriologic media, so negative results were obtained.

Typical lesions with organisms resembling Toxoplasma were seen at postmortem in three of the patients and from a biopsy of the brain in another two. The pathology in these cases differed in no way from that described in the literature.[1] The remaining patients are still alive, and we have had no opportunity to examine their tissues for Toxoplasma; for that reason we have not listed them as proven cases.

Discussion

There are many unanswered problems in this still rather new disease in human medicine, and a great deal more research is needed. The epidemiology is little understood and the problem of latency in human subjects is very disturbing when it comes to the interpretation of their neutralization tests. Considerable progress has been made by Sabin and his associate on the nature of this antibody.[9,13,15] The specificity of the neutrali-

zation test has been questioned seriously by those intimately interested in its evaluation. Heidelman found positive tests in 10 to 14% of persons without clinical manifestations of the disease and concludes from his studies that probably in some of these persons, the reactions are non-specific.[14] Ruchman, on the other hand, feels that the test may be quite specific and may be relied upon particularly in the presence of cerebral calcification or chorioretinitis.[12]

The most important finding in the patients which we have studied has been the almost constant occurrence of internal hydrocephalus. It was present in patients with a normal or small head size as well as in macrocephalus. Cerebral calcification occurred in seven of the patients and chorioretinitis was present in five individuals. Five patients in this study had neither of these cardinal findings and two of these were patients in whom the toxoplasmic organism was found. This evidence strongly suggests that the diagnosis should be suspected if the patient had internal hydrocephalus only. In five of our patients, the diagnosis of toxoplasmosis was established by finding characteristic pathologic lesions and organisms resembling Toxoplasma. However, two of these patients had abnormal spinal fluid findings but none of the other classical findings except internal hydrocephalus.

Evidence that the disease was of prenatal inception was established in three patients. Hydrocephalus requiring cranioclysis in one instance is reported and a skull fracture at birth because of hydrocephalus occurred in another baby. The third patient died at birth and lesions with the toxoplasmic organism were revealed at autopsy.

Summary

Five proven cases of toxoplasmosis in infants and nine cases in which the clinical and laboratory evidence strongly suggested this diagnosis in infants and children are presented.

We have pointed out that only one or two of the cardinal manifestations may be evident in a patient in whom the diagnosis has been established by the finding of the typical pathologic lesions and the organism. This was the case in two of the patients reported, both of whom had internal hydrocephalus but did not have either cerebral calcification or chorioretinitis.

The presence of internal hydrocephalus particularly with spinal fluid changes such as elevated protein and pleocytosis should suggest to the clinician the diagnosis of toxoplasmosis. When the classical triad or tetrad of symptoms and signs of the disease is present and the neutralization test is positive, the diagnosis probably should be made since isolation of the organism from the patient is so difficult at the present time.

Jaundice can be the presenting complaint in a patient with congenital toxoplasmosis.

Addendum

Since this manuscript was prepared, we have had an opportunity to test the sera of patient #9 in our series and her mother for neutralizing antibodies against toxoplasma according to a new method to be described by Feldman and Sabin. With this method, true antibody, which has become inactivated as a result of improper storage of the serum, can be reactivated by activator serum. After using activator serum with the sera from patient #9 and her mother, both were found to contain neutralizing antibodies against toxoplasma.

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Spanish Abstract

Toxoplasmosis en los Niños

Se presentan cinco casos demostrados de toxoplasmosis en infantes y nueve casos en los cuales la prueba clínica y de laboratorio indica claramente esta diagnosis en infantes y niños.

Hemos señalado que solamente pueden verse una o dos de las manifestaciones cardiacas en un paciente cuya diagnosis ha sido establecida por el descubrimiento de lesiones patológicas típicas y el organismo. Este es el caso que se conoce de dos pacientes que tenían hidrocéfalo interno, pero que no tenían ni calcificación cerebral ni coriorretinitis.

La presencia de hidrocéfalo interno particularmente con cambios del flúido espinal tales como alta proteina y pleocitosis deben de indicar al clínico la diagnosis de la toxoplasmosis. Cuando la triada clásica o tétrada de síntomas y señas de la enfermedad está presente, y el ensayo de neutralización es positivo, probablemente habrá que hacer la diagnosis ya que el aislamiento del organismo del paciente es tan difícil en este tiempo.

La ictericia puede ser la queja que presenta un paciente con toxoplasmosis congénita.

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REPLACEMENT TRANSFUSION AS A TREATMENT FOR ERYTHROBLASTOSIS FETALIS

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THE treatment of hemolytic anemia of the newborn often requires support by compatible blood transfusions. In the years before the discovery of the Rh factor, such blood was usually compatible only according to the A-B-O group, and for convenience the patient's father was often used as a donor. This meant the use of Rh-positive blood. It was found frequently at this time that the infants' blood levels tended to fall rapidly even with repeated transfusions. In many such cases the infused Rh-positive cells are destroyed much more rapidly than are Rh-negative cells as shown by Mollison in England and confirmed by us. It seemed best, therefore, as a first step in improving treatment, to use only Rh-negative blood as a means of achieving the highest blood levels for protection of the patient, and this step was logically inaugurated after 1941.

In the more acute and severe cases of erythroblastosis the infant's anemia often progressed so rapidly in the first 48 hours that several small transfusions proved inadequate. In such patients, by recently developed technics, it has been possible to demonstrate that the serum of the baby still contains free maternal anti-Rh agglutinins and that all of the infant's own red blood cells are often completely coated with this antibody leading probably to a more rapid destruction of the infant's cells. The removal of as much as possible of the baby's own blood should theoretically help diminish the damage resulting from the presence of this free and bound antibody in the circulation and in the tissues. Such reasoning led to the trial of replacement transfusion for the treatment of erythroblastosis. Replacement transfusion is not a new procedure in pediatric practice as many of you know, but to perform it in a newborn infant has added difficulty to an inherently difficult technic.

The earlier method consisted of entering the longitudinal sinus and a peripheral vein, or two peripheral veins, or a vein and an artery. These usually required more or less body exposure for a newborn infant on an operating table, often requiring an hour or more for the procedure and this sometimes caused shock-like symptoms from cold and trauma. In addition, the fragile small vessels and a tendency for the blood to clot as it was being removed further complicated the procedure. The intravascular injection of heparin to keep the blood flowing can be dangerous because of existing hypoprothrombinemia, possible platelet deficiency or capillary fragility—all contributing to the bleeding tendency which is so common in the neonatal period. In fact, massive hemorrhage has been found in a few cases of heparinization of a newborn infant.

The pediatrician faced with the prospect of finding vascular channels for transfusion of a recently delivered infant with erythroblastosis cannot help but be attracted to the large and readily accessible vein which presents itself in the umbilical cord. Earlier attempts were made to use this channel as a site for exsanguination, but these were not uniformly successful. The development by Dr. Ingraham of our Neurosurgical Depart-

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Mead Johnson Award address recorded at the Annual Meeting of the American Academy of Pediatrics, December 10, 1947, in Dallas, Tex.

ment and his associates of a bland polyethylene plastic catheter, which could be left in contact with human tissue for long periods of time without harm, overcame some of the major difficulties of exsanguination transfusion technic. The use of this catheter in the umbilical vein has permitted the performance of prolonged replacement transfusion with relative ease and safety. Much of the technic must be acquired through personal experience and handling of the material. These polyethylene catheters are made by a plastic manufacturer and then tested by Dr. Ingraham's surgical laboratory for several weeks to make sure that no irritation results from the intravascular use of this catheter. As originally used the apparatus consisted of the polyethylene catheter which could be easily threaded through the umbilical vein, through either the ductus venosus into the vena cava or occasionally by passing the ductus venosus and lying in the portal vein. The catheter was then attached by means of a needle to a glass tube, a rubber connecting tube and finally to two three-way valves and a 20 cc. Luer-lock syringe. The blood could be exhausted through the first valve as it was withdrawn from the child, the syringe then refilled through the second valve with blood from the donor's bottle and this blood reinjected into the child in alternating maneuvers.

More recently, because of some difficulty with clotting of the blood in the valve and the glass tubing, the apparatus has been slightly modified by omiting the glass tube and the rubber connecting tube, using a longer length plastic catheter and needle and then connecting the two three-way valves directly to the needle. This has helped materially in diminishing the difficulty of clotting and the need for frequent irrigation of the valve and the syringe. These catheters are prepared by immersing them for 18 hours or longer in zephrin alba—1:1000 aqueous solution. In fact, the catheters are allowed to remain in the solution indefinitely until ready for use, at which time irrigation with warm sterile saline is carried out. The catheter is threaded through the umbilical vein and is attached to the needle, then attached to the two tubes, and glass and rubber tubes are attached to the valve and the syringe; the two metal basins are used for purposes of irrigation of the syringe when the blood begins to be a bit thick and the procedure tends to slow down.

One of the advantages of being able to use the umbilical vein is that the patient does not need to be exposed on the operating table and hence can be kept warm in a Hess bed or some similar warming bed for a newborn or premature infant. The baby is placed in the Hess bed which has previously been warmed, the extremities somewhat restrained by towels, and a nurse constantly watches over the infant to make sure that the nasopharynx is kept clear of secretions by suction. Oxygen is administered if necessary. The procedure is carried out through the lower window of the Hess bed when the top has been placed in position. The umbilicus is washed as clean as possible and then cut short so that only about a half inch of cord remains above the skin margin. The catheter is then usually tied relatively easily and, with a syringe attached to the needle at first merely to localize the position of the vessel—either the vena cava or portal vein—where blood will flow easily, some blood is withdrawn. Then the syringe is replaced by the three-way valve—the first valve is connected by tubing to a pail in which the exhaust blood can be placed, and the syringe placed again in connection with the second valve to the bottle of blood. By alternate maneuvers of first removing and next putting in blood 20 cc. at a time, the infant can gradually be exsanguinated and most of its blood volume replaced with relatively little trauma.

One does not need to watch too closely the amount of blood taken at a time since it

is replaced almost immediately and the 20 cc. exchanges do not upset the infant's circulation to any extent that we have noticed. Usually we use about a pint of group O blood or group specific blood of the Rh-negative type in replacing the infant's own blood volume. In the course of about an hour to an hour and a half this 500 cc. of blood replaces by actual measurement between 90 and 95% of the infant's own circulating erythrocytes. In this way, one is able to remove the large part of the infant's red cells, cells coated with maternal antibody which are quite likely to be destroyed later and whatever free antibody exists in the infant's circulation. Occasionally we have used more than 500 cc. in a more desperately ill infant but have seen very little benefit from using as much as 1000 cc. The whole procedure takes between one and two hours and the infant at the end of that time usually is in much better condition than at the start of the procedure.

One or two additional points that are worthy of mention are that the infant is generally given calcium at the end of the procedure, having washed out the tube, in an effort to overcome the possible alkalotic tetany that might result from the use of so much sodium that is in the sodium citrate in the bottle of blood. In addition, too, it may be wise to use prophylactically penicillin and sulfadiazine for 48 hours, and we have done so because of the danger of infection working through this relatively unsterile field—the cord—which cannot be adequately washed at first. The operators are draped sterilely and the patient also protected so that a minimum of possible infection may occur.

Occasionally it is necessary to transfuse such an infant again in the second, third or fourth week because the blood levels have not been maintained adequately throughout this time but we have rarely had to offer more than a single small transfusion in the second or third week to infants that have had a complete replacement transfusion and even this single transfusion has had to be given in less than a quarter of the cases. One immediate advantage we noted is that these infants can be discharged usually with the mother; that is, sometime before the eighth day has passed, whereas previously the average period of hospitalization for infants with severe erythroblastosis requiring multiple transfusions was three weeks or more which meant a danger period, a real danger when secondary infections could complicate the course of the child's hospitalization.

It is important here to emphasize that not every infant with possible erythroblastosis requires replacement transfusion. In fact, even though many of the patients sent to us are referred only because of the possible need for such drastic treatment, in the past year we have so treated only about one out of every eight babies with erythroblastosis which have been sent to us. There should be clear indications for such treatment. Otherwise, serious harm may result needlessly. We insist on having available a specimen of the mother's blood, if we have not followed the mother before delivery, by asking every doctor who refers a patient with symptoms or signs of erythroblastosis to be sure to send the mother's blood along before admission of the child. We can thereby prove to our own satisfaction whether or not the mother has anti-Rh agglutinins which can act on the infant's Rh-positive red cells. Having demonstrated the presence of antibodies in the mother's circulation, further evaluation of the case is based on the following points: the clinical signs of erythroblastosis; that is, anemia, jaundice, edema, splenomegaly and hepatomegaly and other signs that you know so well. We assume that the presence of these clinical signs with antibodies in the mother's circulation implies the need for immediate replacement transfusion.

But even in the absence of these clinical signs certain laboratory evidence may suggest the need for immediate treatment and these evidences are based on our previous experience with such tests. First, one must prove that the baby is definitely Rh-positive and occasionally this is difficult if the baby's cells are completely coated with the mother's antibody. Then, if the baby's cells are coated and the baby has free antibody in its circulation we know from our selected data over several years that such infants quite regularly develop severe symptoms within the second, third or fourth days of life and, therefore, those laboratory signs alone, even in the presence of a relatively normal appearing infant, are sufficient indications, we believe, for replacement transfusion.

The absence of clinical evidences, however, and the absence of these clear cut laboratory findings of free and bound antibody, suggest that the infant will do well enough without such drastic treatment. This has been the basis of our withholding such treatment.

Before analyzing our results, two further points must be made. First, in a disease which has so variable a course as erythroblastosis it may be dangerous to draw conclusions as to the value of any mode of therapy unless one has an adequate controlled basis in past experience to make a comparison and also a sufficient number of cases treated by a single method so that valid statistical information may be obtained. Too often it has been forgotten that some infants with erythroblastosis recover easily with no spectacular treatment even though the mother has had a high titer of anti-Rh agglutinin; others die despite heroic therapeutic measures and that again has no direct relationship to the level of antibody in the mother's circulation. A second consideration is that we have recently received more and more cases diagnosed very early, in fact often anticipated, and an increasing number of the patients have had severe erythroblastosis. Ten years ago we rarely saw an infant with erythroblastosis before the age of 36 hours and the average age of entry was three days. This meant that the sickest infants had already died and the remaining patients were more likely to recover under any form of supportive therapy. At present some of our patients have been practically moribund with severe anemia, jaundice, edema and the other complications all within the first 24 hours of delivery. A few have had erythrocyte levels of a million or less at birth. It is obvious that such patients are in a precarious state no matter how good the supportive treatments.

As a background for an evaluation of our present mode of therapy we have statistics collected over the past 15 years or more. All cases have been observed personally. Prior to 1941, taking all the infants sent to us whether or not we could institute therapy promptly and the therapy was successful, there was a 35 to 40% mortality rate. Between 1941 and 1945 our work became known and, therefore, we possibly had a larger number of children with this disease sent to us. We treated such children with Rh-negative blood, and whether because of earlier diagnosis or more successful treatment, our mortality rate dropped to 30% or slightly less. Between 1943 and 1946 again possibly because of better diagnostic procedure, but also possibly because during this time the obstetricians became accustomed to looking for the disease, for antibodies in the mother and also delivering the baby two to three weeks before term, thereby saving infants that might otherwise have been stillborn in the last few weeks, our mortality rate dropped. With Rh-negative transfusion, our data at this time showed about a 20% mortality rate.

We are still somewhat hesitant about drawing conclusions from our present data which now covers about 15 months of experience and 95 infants treated personally by replacement transfusions. The first ten were transfused by various routes; that is, using two peripheral veins or the longitudenal sinus and a vein. The last 85 had been transfused

only through the umbilical vein using this plastic catheter. One other point is very important and has convinced us of the value of this treatment in many instances. Of the 95 cases, 20 occurred in families where a previous child had died with erythroblastosis. In such families, the chance of a subsequent infant's survival is less than 10% in our statistical analysis. Yet, in these 20, 14 infants survived, completely well without any residual damage. Two died and four lived but showed evidence of kernicterus later. In other words, 70% recovered completely, rather than the previous recovery rate of about 10%. Of the 85 infants treated by umbilical vein replacement transfusion, 65 are now living and well and show no evidence of residual damage even after repeated, careful examination—some of them right up to 15 months; all of them over three months.

Seven patients died, but not of erythroblastosis. The causes of death in these children were prematurity or immaturity, congenital atelectasis of the lungs, massive cerebral hemorrhage due to tentorial tears and other factors, which cannot be directly related to erythroblastosis. Seven patients died of the disease despite early or immediate transfusion. Six patients showed kernicterus. We feel at present that kernicterus is not avoided by this mode of therapy since our statistical data is just as poor by this mode of therapy as it formerly was; that is, so far as we know the incidence of kernicterus has not been materially affected since it is not apparently dependent upon anemia and therefore one could hardly expect successful transfusion treatment alone to prevent this disturbing complication. Our statistics, therefore, show close to a 90% recovery rate in comparison to a previous 80% recovery rate at its best and this despite the fact that we are being presented with poorer and poorer specimens considering the severity of the disease and other facts for operation.

I wish to point out that this mode of therapy first has the advantage of ease and greater safety in performance. Many physicians who have previously been unable to transfuse one of these babies by scalp vein or peripheral vein use have carried out this procedure relatively easily. Secondly, and an added advantage, is the earlier discharge of the patient from the hospital at seven or eight days, rather than at two to three weeks. We feel we have saved a certain number of the babies that appeared gravely ill at or shortly after birth, particularly in families that have formerly lost such infants; and, finally, it seems obvious that although this is not a panacea for erythroblastosis it does offer a definite advance in the mode of handling these cases. As an indication of possibly future beneficial therapy, we all agree that the most successful treatment would consist of prevention rather than merely the repair of hemolytic anemia of the newborn. This would require the prevention of antibody formation in the mother or the neutralization in the mother and in the infant of the anti-Rh agglutinins already present. But, until such specific cures can be developed, replacement transfusion seems to be a better method of treatment for many cases of erythroblastosis.

SPANISH ABSTRACT

Not available for publication.

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ACUTE DIARRHEA IN INFANCY

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THIS term—acute diarrhea in infancy—has in English speaking countries a rather precise meaning, characterized, besides by the gastro-intestinal symptoms of vomiting and diarrhea, by an impairment of the aqueous metabolism (dehydration). This picture corresponds to the akute ernährungstörung, toxikose, somerdurchfalle, brechdurchfalle, of the German writers. These terms and the corresponding syndrome have given rise to an extensive literature attempting to classify and divide these entities; such as, acute nutritional disturbances, parenteral diarrheas, enterocolitis or dysentery-like diarrheas, enteral diarrheas, etc. We believe such an extensive subdivision has no practical value; and, furthermore, it makes difficult the understanding of the problem. Diarrhea in infancy is a symptom or reaction to the most varied etiologies, going from the simple underfeeding or anomalous diet or hygiene to a real dysenteric infection.

We have included in the present study only those cases of acute diarrhea in infants, characterized by a sudden onset and accompanied by a systemic reaction such as fever, etc., attributable directly to an infection or secondary to a general metabolic disturbance, such as dehydration, acidosis, coma, etc.

We believe all the acute diarrheas in infancy have an infectious origin, as was stated by Czerny several decades ago. Should the specific infection come from the outside (shigellas, salmonellas, etc.), from intestinal saprophytes causing alteration of the normal flora and chyme, or from a parenteral focus, such as otitis, pneumonia, pyuria, a similar clinical picture always develops as far as severity and symptomatology is concerned. The predominance of any one of these etiologic factors is just a matter of locality, sanitary conditions, previous health status, season of the year, etc. The mechanism by which so many different sources of infection cause so similar clinical and anatomic pathologic pictures is not quite clear.

The fundamental concept of etiology in infant diarrhea has not changed much since the early works of Moro, Adam and Bassau, who described the role played by Esch. coli and its invasion of the upper intestine, or those dealing with primary alteration of chyme, B. perfringens, pyocyaneus, Str. fecalis, until the more modern concepts of the etiologic importance of other micro-organisms such as salmonellas, p. morgagnii, etc. Very important foward steps in the handling of these cases have been made since the advent of sulfa drugs; the success attained by this new method of treatment confirms the importance of infection in its etiology.

Two dominant elements should be considered by both the clinician and the sanitary physician in dealing with acute diarrhea in infancy: first, the etiologic factor of infections; second, the metabolic disorder coexisting or secondary to it. A knowledge of the exogenous factors as causative agents of diarrhea in infancy, will lead to an adequate approach in the individual case as well as in the population. The severity of a given case is indicated by the metabolic impairment.

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At our hospital we designate these syndromes by the nutritional or metabolic disorder (dyspepsia, toxicosis) followed by the name of the etiologic agent, if known, or demonstrable by clinical or laboratory means (dysenteric enterocolitis, parenteral diarrhea due to otitis, pneumonia, etc.)

Based on these premises we think the acute diarrheas in infancy can be separated in two groups: 1. Those without any clinical metabolic involvement (such as the diarrheas due to underfeeding, transitory diarrhea of the newborn, etc.), and 2. Those acute diarrheas accompanied by systemic or metabolic reactions and infection. The present work deals only with the latter. We have studied the cases from two different angles considering these different qualities. Our observations are based on a study done for the past six years at the Luis Calvo Mackenna Hospital, Santiago, Chile, which has 150 infants' beds.

The first group consists of 1505 infants who had one or more (but separate or independent) acute diarrheal episodes, amounting to a total of 3391 episodes. These have been studied from the standpoint of etiology, clinical evolution, mortality and relationship between etiology and clinical picture. We secured this material in a period of six

TABLE I

ORIGIN OF ACUTE DIARRHEA IN INFANCY IN 3,391 EPISODES

Enteral infection	210
Parenteral infection	3,020
Non-demonstrable infection	161

years and all the patients had a similar regimen, surroundings, treatment and handling by the same personnel.

The second group is made up of 199 infants selected in a period of one year who had acute diarrhea with stools containing mucus, pus and blood, who underwent a thorough laboratory investigation to demonstrate the causative micro-organism.

In the first and larger group we have included all those cases of acute diarrhea whatever the origin might have been: enteric infection, parenteral infection, and those cases where no infection was demonstrated clinically by laboratory or postmortem examination in the fatal cases.

Cases of enteral diarrhea are those in which the infection is supposedly intestinal in its origin, has a sudden onset with stools containing mucus, pus or blood, is due to a specific micro-organism demonstrable by bacteriologic investigation (although in this study very often none was isolated), and there is no other infectious focus elsewhere in the body. In this group we included 210 diarrheal episodes.

Cases of parenteral diarrhea are those in which the diarrhea precedes, accompanies or follows a determined extraintestinal infectious process, without any specific intestinal micro-organism revealable by stool investigation and where the autopsy of those fatal cases usually shows the extraintestinal focus. In this group belong most of the cases of diarrhea and in our study they amount to 3,020 episodes.

Finally there is a third group in which neither the clinical symptomatology at the onset and evolution, nor the bacteriologic studies and postmortem examination of the fatal cases shows any intestinal or extraintestinal infectious process. In this group we count 161 cases (Table I).

Notwithstanding the predominance of the cases of acute parenteral diarrhea, it is

noteworthy that the great majority are present in spring and summer months—2,225 episodes out of 3,391. (Table II). As it will be shown later on, this phenomenon is even more striking in enteral diarrheas.

TABLE II

SEASONAL DISTRIBUTION OF ACUTE DIARRHEA IN 3,391 EPISODES

Summer	1,279	2,255
Spring	976	
Winter	558	1,036
Autumn	478	

Age: The age of the infants was distributed as follows: under one month, 100 cases; from one to 24 months, 1,405 cases with one or several episodes.

Previous Nutritional State: A factor of the foremost importance in the etiology of acute diarrhea is the previous nutritional status of the child (Table III). The great majority (1,149 out of 1,505) suffered from a chronic nutritional disturbance which predisposed them to acute diarrheas of a more severe nature.

TABLE III

PREVIOUS NUTRITIONAL STATE OF 1,505 INFANTS WHO HAD ONE OR MORE ACUTE DIARRHEAL EPISODES

Eutrophy (normal)	356	
Dystrophy	1,024	1,149
Atrophy	125	

Out of this total of 3,391 diarrheal episodes, there was a coexisting acute metabolic disturbance in 2,060 cases (60.7%) and it was manifested by a body weight loss, fever, dehydration, acidosis and lowered nutritional tolerance; this picture corresponds to the so-called dyspepsia or toxicosis of the acute nutritional disturbances. It is noteworthy that this syndrome was present in almost the entire group we called enteral diarrhea (210 cases) excepting only three cases.

MORTALITY AND PATHOLOGY

Out of the total of 1,505 infants who had one or more diarrheal episodes, 256 (17%) died in the six year period of observation. If we refer our mortality rate to the total of 3,391 diarrheal episodes the rate is only 7.54%.

A postmortem examination was performed in 244 of 256 fatal cases. Intestinal lesions of different degrees ranging from simple inflammation of the mucosa to ulcero-hemorrhagic lesions were found in only 89 cases. Forty-two of these 89 cases had had stool examination with positive results in only 12 (shigella or salmonella) (Table IV).

The sub-group of 210 cases denominated here as enteric diarrhea deserves special comment. All these cases were investigated bacteriologically, and in only 67 (31.9%) was a specific diarrhea-producing germ isolated from the feces: 55 shigellas and 12 salmonellas. As we will see further on, this same percentage appears in another group which was specifically investigated from a bacteriologic standpoint.

The lethality reached in this sub-group was 30%, a much higher figure than the total found in the whole working material. It is also remarkable that no parallelism exists between the type of diarrhea showing inflammatory characteristics (pus, blood, mucus), and the pathlogic findings. In the 67 cases in which the presence of enteric germs was demonstrated, only 55 had inflammatory stools.

The second group of patients in our study consists of 199 infants who suffered from acute diarrhea of an inflammatory type who were observed during the 1944-1945 period at our hospital. All of them were thoroughly investigated from a bacteriologic standpoint directed to isolate specific enteric germs, such as shigella and salmonella. A parasitologic study was also performed in each case. The culture media employed were: desoxycholate-citrate agar (Leifson's medium), brilliant green-eosin agar (Kristensen, Lester, Jurgens medium), and lactose-agar with bromcresol purple, as indicator. For the isolation of doubtful colonies the Krumweide, Surraco and Pereira media were employed.

In 107 (56%) out of the 199 infants the acute enteric diarrhea was accompanied by

TABLE IV

Deaths: 256		Intestinal lesions		Bacteriologic stool investgation in cases with intestinal lesions	
		Found	Not found		
Autopsy	No autopsy			Was performed in	Was not performed in
244	12	89	155	42	47
				Specific germ discovered	No specific germ discovered
				12	30

an acute metabolic disturbance as formerly stated. This figure is similar to that found in the first group of 3,391 diarrheal episodes of different origin where the frequency of the metabolic disorder appears in 60.7%.

In both groups the highest incidence of acute diarrhea appears in November and December (late spring): 57 cases in November, 48 in December, and 18 in January. This higher late spring incidence was also noted in a previous investigation done by one of us (Garcés) who in 404 cases of shigella infections in Santiago found 15.6% of them in October, 24.5% in November, 24% in December, and 7.4% in January (mid-summer). This fact reveals a definite parallelism between the highest incidence of specific enteric infection as demonstrated by bacteriologic investigations and the frequency and severity of acute diarrheas in infants during the late spring and early summer seasons, which, of course, cannot be exclusively blamed on the pathogenic germs.

In the group of 199 infants a shigella was isolated in only 55 cases and a salmonella in 12, giving a total percentage of 33.6% of specific enteric infection, which is very similar to that 33.9% of those 210 formerly commented on cases. In some of our previous studies on dysenteric diarrheas (Garcés, Ariztía), we succeeded in isolating the infecting germ in a higher percentage (53%).

In 28 of these 199 cases the presence of a protozoa was discovered: three Entamoeba histolytica, 11 Lamblia intestinalis, and other protozoa to which we do not give any important etiologic significance in the acute diarrhea.

Comment

From an analysis of two groups of cases, it may be deducted that it is not always possible to separate in different clinical entities the acute diarrhea in infants based only on the bacteriologic or pathologic findings, the character of the stools with or without inflammatory elements, and trace a sharp separation between enteric or parenteric diarreas and simple metabolic disturbances. It has been demonstrated that even in those inflammatory diarrheas an enteric germ can be isolated in only 30% and that this type of diarrhea might be present even in cases where an evident parenteric infectious focus is demonstrable, such as otitis, pneumonia, etc. On the other hand, the same intestinal lesions may be found in specific dysenteric diarrheas and in others which are not, and that no lesions may be discovered in clearly proved dysenteric cases.

However, we have to recognize that the clinical findings alone may in extreme cases predict with certain accuracy the specific nature of a diarrhea or the presence of a parenteral process through a careful observation of the systemic reaction, characteristic inflammatory stools or by the demonstration of the extraintestinal focus.

Nevertheless, it seems questionable to ascertain whether the parenteral infection (streptococcal, pneumococcal, etc.) is indirectly or systemically responsible for the enteric reaction (parenteral infection) or whether this is due to a local response to the pathogenic organisms and their toxins acting upon the intestinal wall (enteric infection).

The practical value of this differentiation between specific enteric and parenteric infections depends on their differing response to chemotherapeutic agents: sulfaguanidine and sulfasuxidine being used in the former and sulfadiazine, sulfathiazol or penicillin in the latter.

Although we have not tried to summarize in this paper our therapeutic results with those drugs, from previous investigations we can now affirm the mortality rate in acute diarrheas has been lowered at least 30% to 40%, their seriousness has been considerably lessened, and the hospital stay period shortened.

Diagnosis

From a practical and diagnostic standpoint we think it of the greatest importance for the attending physician to understand the true role of the metabolic impairment in view of a correct and early treatment of dehydration and acidosis and thus avoid further damage of the organic parenchymae. Furthermore, the knowledge of the possible etiology orientates the specific therapy with the most appropriated drug (sulfaguanidine, penicillin, etc.) to the right place (enteral or parenteral).

Finally, a thorough bacteriologic investigation should be done in every case to determine the role played by the different specifically enteric germs in the etiology of acute diarrheas.

Prophylaxis

In dealing with acute diarrhea in infancy there are two points worth considering. First, the preservation of a good nutritional state through an adequate diet and appropriate hygienic measures to protect the child from infections. We have already seen how important this previous health status is since diarrheas are so much more severe in the undernourished children. In this country we have observed a much lower morbidity and mortality rate among those children who are cared for at public and private health centers than those who are not. Secondly, the aggregated sanitary measures tending

to avoid the enteric infections such as milk, food, water, sewage controls and the elimination of carriers which seem to be so important, since there is a very clear relation between the outburst of acute diarrhea in infancy and the demonstration of specifically enteric germs in adults or other children. The early diagnosis and treatment of the less severe or incipient forms of dysenteric infections as well as the education of parents and guardians as far as elementary hygiene and scientific handling of the baby are concerned, appear to be of foremost prophylactic importance.

Treatment

We must again emphasize the differentiation between the metabolic involvement and the infectious factor in any given case of diarrhea. The former is characterized clinically by dehydration, acidosis and intrinsic starvation caused by accelerated loss of intestinal content and lowered nutritional tolerance which makes it difficult or prevents any attempt to feed the child since alimentation would lead only to aggravation of the clinical picture.

If vomiting is not too prominent we try to hydrate the patient giving him only fluids by mouth 150 to 200cc./kg. body weight daily. If it happens that oral administration is not practicable, we give the same amount of fluids parenterally; usually a mixture of equal amounts of physiologic saline and 5% glucose intravenously by slow drip (30 gtts./min.).

We continue this fasting or elementary liquid diet period no longer than 10 to 12 hours and give then the so-called "hydrating diet" with carbohydrated solutions (mixtures of equal amounts of saline, rice paste and 6% dextrimaltose, or combination of buttermilk, whey, rice paste and 6% dextrimaltose). Of these 'hydrating diets" we give only 50 cc./kg. the first day, supplementing the basal liquid necessity with simpler solutions; the second day we give 100cc. and 150cc. the third.

Thus we combat the dehydration and acidosis, being able to prolongate the waiting period until the nutritional tolerance is improved and not being afraid of starvation.

Afterward we start re-feeding the child according to his age and previous nutritional condition with progressive amounts of buttermilk or human milk as to reach a calorically normal diet within a week.

As laboratory control of the exicosis, we check the blood protein level, refractory index and blood cell counts, and administer blood or plasma transfusions according to necessity and if dehydration is not too marked.

As far as infection is concerned, we try first to determine its nature and origin in order to use the most appropriate form of therapy. In enterocolitis and dysentery-like diarrheas, we prefer to use sulfaguanidine or sulfasuxidine since they are better tolerated and are not absorbed from the intestinal tract. In parenteral infections we prescribe general-acting sulfa drugs such as sulfadiazine or sulfathiazol; if we are dealing with a penicillin-sensitive organism, we also use this drug.

Conclusions

An analysis of acute diarrheas in infancy is made, based on the clinical study of two groups of patients: the first is made up of 1,505 infants who had 3,391 diarrheal episodes in a period of six years; and the second, of 199 infants who had a dysentery-like diarrhea in a period of one year's observation.

Out of the 3,391 diarrheal episodes 3,020 showed an infection of parenteral origin, 210 enteral, and 161 no demonstrable infection.

We consider every acute diarrhea in infancy as having an infectious origin either parenteral or caused by specifically enteric exogenous germs as well as the nonspecific intestinal flora.

In the great majority of our diarrhea cases (2,060 or 60.7%) there was a coexisting metabolic impairment and this was almost general in the enteral infection group, having a mortality rate of 17%.

The isolation of a specific enteric germ (salmonella, shigella) was only possible in approximately 30% in both groups, the first one with 210 cases of enteral infection, and the other of 199 children with dysentery-like diarrhea.

The highest incidence of diarrhea in this country is in spring and summer seasons. Most of the affected children were previously undernourished.

Postmortem examinations in fatal cases failed to show a relationship between the severity of intestinal lesions and the type and origin of the infection. Neither could we demonstrate a definite parallelism between cause and character of the diarrhea, although specific enteric infections had certain predominance of inflammatory stools (salmonella, shigella).

From a diagnostic, therapeutic and prophylactic standpoint, we have indicated the importance of two main elements in any given case of diarrhea: its metabolic impairment and the infectious etiologic factor. We think neither element alone justifies the denomination and classification of acute diarrhea in infancy.

The preservation of a good nutritional state and the sanitary control of food, water. sewage, etc., as well as the elimination of carriers, seem to be of the foremost prophylactic importance.

In the individual case treatment should correct the metabolic impairment and infection.

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Spanish Abstract

Diarrea Aguda del Lactante

En el trabajo se empieza por definir el concepto de diarrea aguda del lactante el cual comprende un sindroma que presenta perturbaciones agudas gastro intestinales, acompañadas de alteraciones

generales del organismo tales como fiebre, deshidratación o acidosis, etc. que derivan ya sea del proceso infeccioso desencadenante del sinroma o de la perturbación metabólica, especialmente del metabolismo acuoso, que él provoca. Se considera que toda diarrea aguda del lactante deriva de una infección: ésta puede ser de origen paraenteral o enteral, pudiendo esta última ser causada por gérmenes exógenos entéricos (Shigellas, Salmonellas, etc.) o por exaltación de la flora endógena intestinal.

Se estima que en toda diarrea aguda del lactante hay dos factores primordiales que debe siempre tomar en cuenta el médico en el diagnóstico, la profilaxia y el tratamiento; el trastorno metabólico acompañante de la diarrea y el factor etiológico infeccioso.

El trabajo se basa en el análisis de un material formado por dos grupos de enfermos: el 1° lo constituye un grupo de 1,505 lactantes que durante un período de observación de seis años presentaron 3,391 episodios diarreicos separados entre sí, y que tuvieron diversas causas: infección paraenteral, enteral o sin origen infeccioso aparente. Este grupo se analiza desde el punto de vista de la etiología, manifestaciones clínicas, mortalidad y hallazgos anátomo patológicos, para establecer si existe relación entre esos hechos que permita una nomenclatura o clasifiación de las diversas diarreas agudas del lactante.

El segundo grupo está constituído por 199 lactantes que presentaron diarrea aguda de tipo enteral durante un año de observación y que fueron específicamente investigados desde el punto de vista bacteriológico.

En el primer grupo de 3,391 episodios diarreicos se observa al través del estudio clínico, del laboratorio y anatomía patológica, que en 3,020 casos de diarrea tienen un origen de infección paraenteral; en 210 casos un origen enteral, y en 161 no se comprueba origen infeccioso aparente.

El mayor número de niños afectados por diarrea aguda en este grupo, sufrían anteriormente de trastorno nutritivo crónico (distrofia).

En más del 60% de estos casos la diarrea aguda se acompañó de trastorno metabólico agudo.

La mortalidad de este grupo alcanza al 17% del número de niños estudiados. La autopsia practicada en 244 de los 256 fallecidos no demuestra relación entre las lesiones encontradas y el origen de la infección o causa de la diarrea. Tampoco se observa paralelismo entre el tipo de deposiciones y el origen de la infección (enteral o paraenteral).

Tanto en los 210 casos, considerados como diarrea de origen enteral en el primer grupo, como en los 199 casos del segundo grupo, estudiados bacteriológicamente, sólo se logran aislar gérmenes entéricos (Shigellas o Salmonellas) en un 30%.

En ambos grupos se observa que la mayor frecuencia de aparición de las diarreas se presenta en los meses de primavera y verano.

De este estudio se deduce que no es posible ni conveniente en la práctica establecer una nomenclatura o clasificación de las diarreas agudas del lactante, basadas en la causa infecciosa, o en el caracter de la diarrea o el hallazgo anátomo patológico.

Para la profilaxia de las diarreas agudas del lactante se insiste en la importancia de la mantención del buen estado nutritivo de aquél mediante la asistencia preventiva, junto a las medidas profilácticas sanitarias de control de aguas, alimentos, etc. como la investigación y separación de portadores de germenes disentéricos para el cuidado del lactante.

En el tratamiento del caso individual se insiste también en la importancia de la dietética y medidas para reparar el daño metabólico causado por o acompañante de la diarrea aguda, junto a la terapéutica anti infecciosa y quimioterapia.

A. Vargas 248.

THE RECOGNITION AND TREATMENT OF INCREASED INTRACRANIAL PRESSURE IN INFANCY AND CHILDHOOD

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THE classical symptoms and signs of increased intracranial pressure may be recognized in the adult with a fair degree of accuracy. They consist, briefly, of headache, vomiting, the appearance of papilledema and a depressed or altered state of consciousness. They appear in the presence of any expanding lesion, be it brain tumor, traumatic hematoma or chronic infection, because of the relatively simple fact that the adult skull may be considered a closed box, incapable of significant expansion in terms of relief of intracranial hypertension.

This famous closed box theory upon which almost all the methodology of neurologic surgery depends was presented first by Monro and Kellie and was later modified to include the cerebrospinal fluid by Burrows. In the era of modern neuro-surgery the work of Dr. Lewis H. Weed[1] has further refined this theory to include chiefly the stretch component of the inner confining membrane of the closed box, the dura mater.

In essence, the closed box theory of this long list of distinguished investigators states: (1) that the skull, pierced but by minor foramina, may be considered inexpansible, (2) that within the skull, brain tissue, arterial and venous circulating blood and cerebrospinal fluid rest in equilibrium influenced in the normal state only by postural head and body changes, (3) that any change such as that of an expanding brain tumor in the relative volume of these components of the closed box must be compensated for by a change in one or all of the constituents, and (4) that when the limits of this normal compensatory mechanism are attained, since the closed box can no longer expand, signs of increased intracranial pressure will develop (Fig. 1). Normal intracranial pressure in the adult is, in simple terms, a measure of the pulsating arterial systolic pressure, an unimpeded venous outflow, a stable brain volume, the normal production and absorption of cerebrospinal fluid and a solid inexpansible skull.[2]

Identical factors operate in the maintenance of normal intracranial pressure in the infant or child although they may be envisaged as progressively changing factors due to the growth of the central nervous system and its envelope, the skull. In a consideration of intracranial hypertension in the infant and child, the closed box theory, so dependable and so static in the adult, must now be critically scrutinized since there is a normal growth increment in brain volume, and due to open fontanelles and unfused suture lines, the skull is an expansible box rather than a closed box. The average weight of the brain of the newborn infant is 350 gm. and this weight may be more than doubled at nine months and trebled at three years. At the age of two years, the brain is approximately four-fifths the adult size. The brain grows then more gradually until the age of 15 years to an average weight of 1340 gm., although there are striking individual differences (Fig. 2).

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Read at the Eastern Areal Meeting of the American Academy of Pediatrics, Buffalo, N.Y., May 1, 1948.

(Received for publication May 24, 1948.)

Skull growth progresses in a similar fashion and may be correlated with body weight, height and chest measurement.[3] The cranial suture lines unite at the age of six months and begin to close at an age corresponding to the period of cessation of brain growth; six fontanelles are present at birth, remaining open to the age of 12 to 18 months.

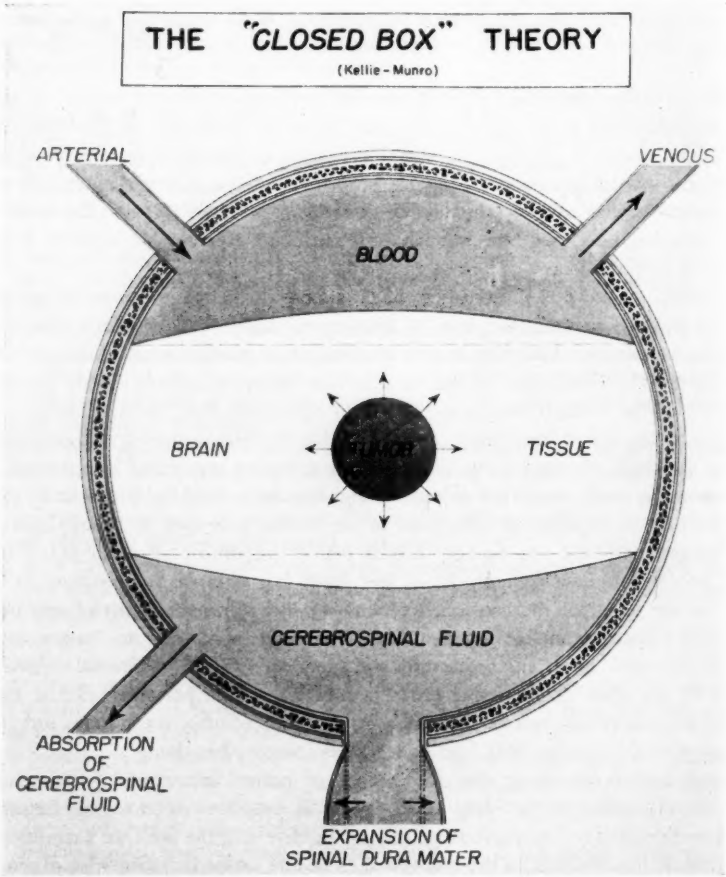

FIG. 1

In view of these remarks, the normal roentgenogram of the skull of the infant and child will be expected to show definite differences from that of the normal adult, differences which are significant in the neurosurgical search for evidence of increased intracranial pressure. In the infant, the bones of the skull appear homogenous, since they lack a diploic structure and lack as much inorganic material as adult bones. The bones are thin and fail to exhibit vascular markings and irregular areas of rarefaction or density characteristic of the adult skull roentgenogram. Suture lines, being composed of fibrous tissue, are well marked and wide. The sella turcica is roughly circular, smaller than that

of the adult and shows a blunt dorsum sella. At the age of 10 months the characteristics of the infant skull are still obvious. After the age of two years, a diploic structure appears and the skull roentgenogram begins to approach that of an adult. By comparison with that of the infant, the tremendous increase in brain volume is readily appreciated (Fig. 3.). The bones of the skull gain adult thickness slowly and a striking

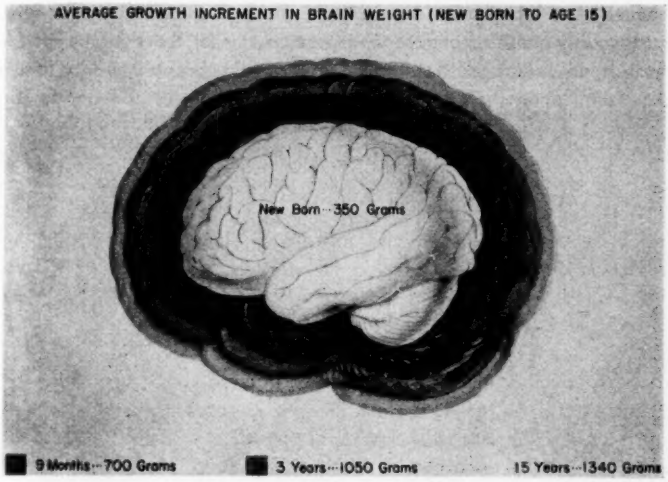
AVERAGE GROWTH INCREMENT IN BRAIN WEIGHT (NEW BORN TO AGE 15)
New Born--350 Grams
9 Months--700 Grams
3 Years--1050 Grams
15 Years--1340 Grams

FIG. 2

FIG. 3. Normal skull roentgenograms of two year old child (left) and one month old infant (right) showing increase in brain volume.

manifestation of the growth curve of the child's brain is apparent as a mottled irregularity on the inner surface of the skull. These areas corresponding to the convolutions of the growing brain are known as digital or convolutional markings. They may be irregularly distributed or localized. Within certain limits, these markings must be regarded as normal findings in the X-ray of the growing child's skull.

Intracranial hypertension in infants and children has its origin in roughly three

groups of abnormal conditions, and these may be divided for purposes of discussion into congenital, neoplastic and traumatic sources. The marked difference between the closed box theory as applied to children and to adults is perhaps most vividly illustrated in a consideration of congenital hydrocephalus. As noted above, the open fontanelles, the fibrous suture lines and the thin cranial bones form weak links that give way under the expanding intracranial pressure. Fontanelles bulge and widen, suture lines separate, and individual cranial bones balloon to portray the characteristic hydrocephalic head. Thus, an expanding skull circumference represents one of the signs of increased intracranial pressure in infants and children, and it will present itself in greater or less degree, depending upon the age of the patient and the force and the duration of the internal pressure. Although an enlarged head will be noted most frequently and in its most dramatic form in hydrocephalus due to congenital obstruction of the cerebrospinal fluid pathway, it can be recognized in other conditions in which a chronic and progressive form of intracranial hypertension exists. Moderate degrees of head enlargement may be recognized in subdural hematoma and intracranial tumor developing in age groups particularly under those of three to five years, and are proven by comparative measurements with standard head circumference charts. When such lesions as congenital stenosis of the aqueduct of Sylvius are recognized later in life, the head enlargement may be of considerable magnitude.

Another form of congenital malformation seen in infants and young children illustrates quite well, although in a different fashion, the relationship among the factors of growing brain, suture line closure and thin skull bones which we have noted as qualifying the conception of the adult closed box or inexpansible skull. This malformation has to do with the premature closure of all suture lines, the so-called craniosynostosis. Variations of the total form of closure are seen clinically, but have little to do with our present discussion. In this condition, the growing brain encounters not a box expanding because of open suture lines, but a closed box similar to the adult skull, except for normally thin cranial bones. As a visible feature of the resulting rise in intracranial pressure due to brain growth the convolutional pattern of gyri and sulci are literally imprinted on the inner surface of the cranial bones (Fig. 4). Descriptive terms of convolutional atrophy and the hammered silver appearance have been given to this roentgenographic evidence of increased pressure. A host of clinical variations exist, but the classical form of oxycephaly may be readily recognized by the characteristic round, turret-shaped skull. In some children, a parrot face, prominent eyes and prognathism complete the clinical picture. A secondary decrease in volume of the orbit due to collapse of the supraorbital surfaces may cause actual protrusion of the orbital contents. Following craniectomy, the marked separation of the surgically manufactured suture lines will demonstrate again the marked degree of intracranial pressure that may be present in this malformation. Gradations of convolutional atrophy may be seen in X-rays of the skulls of children with elevated intracranial pressure and in particular in those children with brain tumor. It is difficult in many instances to differentiate between the imprint of the normally growing hemispheres and that of convolutions under increased pressure. When the intracranial pressure is associated with ventricular distention, as it often is, the sella turcica may be eroded by the downward pressure of the floor of the third ventricle.

To enlargment of the head, convolutional atrophy and erosion of the sella turcica must be added a fourth and very common sign of increased intracranial pressure; namely,

separation of the suture lines. This pathognomonic evidence of pressure may be discovered by both clinical and roentgenographic studies.

In 1893, William Macewen, a Scotch neurosurgeon, wrote a book entitled "Pyogenic Infective Diseases of the Brain and Spinal Cord," a treatise that may still be read with profit.[4] There is a chapter sub-headed, "The percussion note in over-distended lateral ventricles," in which the author describes the so-called cracked-pot or Macewen sign elicited by digital percussion of the child's head. The matter is concluded in brief fashion by the statement: "The facts here adduced indicate that a field, though a limited one, exists in which the elicitation of a differential percussion note is of diagnostic

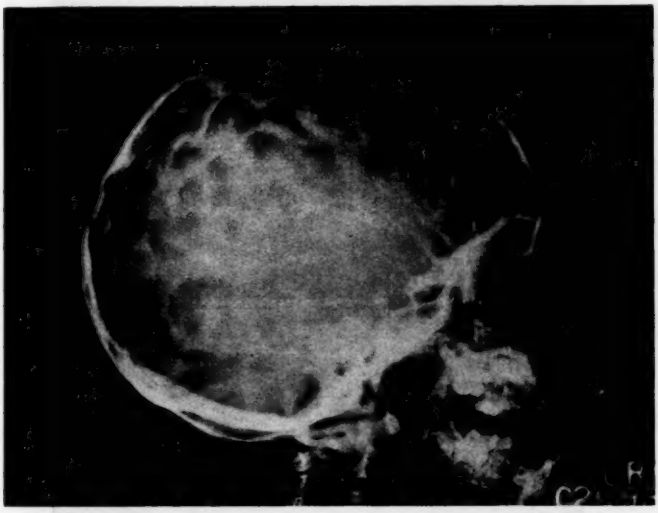

FIG. 4. Marked convolutional atrophy of advanced craniosynostosis.

service when carefully considered along with other data. The obscurity of cerebellar lesions at an early stage and especially in children is such that every point which assists in their detection is of value." Most neurosurgeons would agree with and amplify this conclusion by stating that the finding of the cracked-pot sound represents one of the most simple and most valuable clinical aids to the diagnosis of intracranial pressure in children.

X-ray studies of the skulls of those children in whom the cracked-pot sound is elicited will almost invariably show distinct separation of the suture lines. This may be seen in lateral views of the skull where the coronal suture line is commonly more affected and in anterior-posterior views where the sagittal, rather than the lambdoidal will separate more widely (Fig. 5). One would expect perhaps that the various X-ray evidences of increased pressure would appear simultaneously in every patient. That is not the case however, due to age differences and to variations in the degree of pressure, the thinness of the skull, the fibrous fixation of the suture lines and the presence or absence of ventricular hydrocephalus. The most valuable single sign is that of separated suture lines.

Although the fundamental differences between the skulls of infants and adults influence

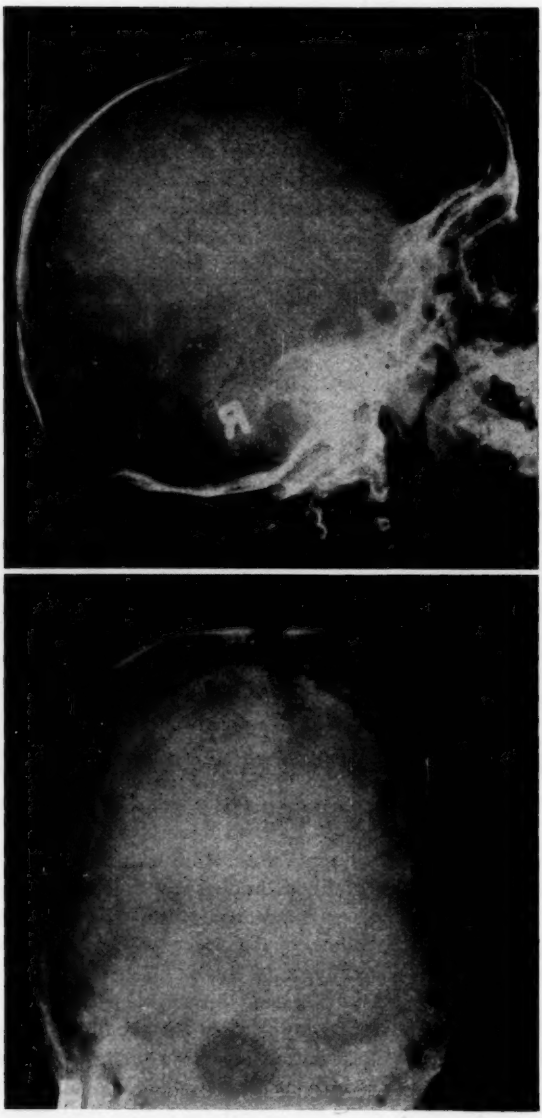

FIG. 5. Separation of coronal (top) and sagittal (bottom) suture lines in increased intracranial pressure due to brain tumor.

the X-ray diagnosis of increased intracranial pressure in the former group, the clinical signs and symptoms of intracranial pressure are identical in both and equally as characteristic. They often appear however in children in almost a fulminating fashion and may be interpreted, as is well known, as representing diseases quite unassociated with the central nervous system.

In order to evaluate the symptoms and signs of intracranial hypertension in the age group below 14 years, a series of 100 verified brain tumor patients was studied from these points of view. There were 55 male children and 45 female, 70 white and 30 Negroes and their age distribution is noted in Chart I. This chart of age incidence is almost identical with that portrayed in Bailey, Buchanan and Bucy's monograph on this subject, a classical study in this field.[5] The time of onset of the initial symptom of increased pressure or neurologic defect is again charted, Chart II, and it is obvious that a major percentage of these patients presented a short, almost fulminating history of onset prior to hospitalization. One may infer from this that the compensatory mechanism of skull expansion has prevented subjective distress during the early phase of increasing pressure and that symptoms develop only when intracranial pressure is well advanced and the compensatory mechanism has failed.

The types of initial complaint in this group of tumor patients were almost equally divided between those suggesting a reaction to intracranial hypertension and those denoting a specific neurologic defect. Thus 49 of this group demonstrated headache, vomiting or an enlarged head as the initial complaint and 31 described a staggering gait or an extremity paralysis as the initial symptom.

INITIAL COMPLAINT

Headache	39	Convulsions	6
Staggering gait	19	Squint	5
Muscle weakness	12	Visual loss	5
Vomiting	8	Other	7

When the general symptomatology of the preoperative course of this group of brain tumors was investigated, it was noted that a very large percent showed the syndrome of headache, vomiting and disturbance of vision that is so characteristic of intracranial pressure. Since a large proportion, perhaps 70% of intracranial tumors in children involve the cerebellum or brain stem, the complaints of staggering gait and cranial or peripheral motor weakness might well be expected.

SYMPTOMS

Headache	79%	Dimness, vision	29%
Vomiting	81%	Motor paralysis	29%
Staggering gait	59%	Sensory loss	0%
Squint	24%	Pain, cervical	14%
Tonic convulsions	10%		

The neurologic examination of a child suspected of harboring a brain tumor may be divided into: a search for evidence of intracranial hypertension; and an evaluation of the existing neurologic defect. When these factors were analyzed in this set of verified brain tumors, it was found that 88% gave indisputable evidence of increased pressure through simple ophthalmoscopic examination of the eyegrounds. (Fig. 6 and 7) The lesson is obvious that the ophthalmoscope should be used by pediatricians as often as is the otoscope. An enlarged head and the so-called cracked-pot sound were present in significant numbers of patients. The evidence of neurologic defect was strongly pointed toward the common sites of tumor origin, the cerebellum and brain stem. When the plain or routine X-rays of the skulls of these patients were examined, it was apparent that the diagnosis of a neoplasm could be suspected if not proven in 63% of the children.

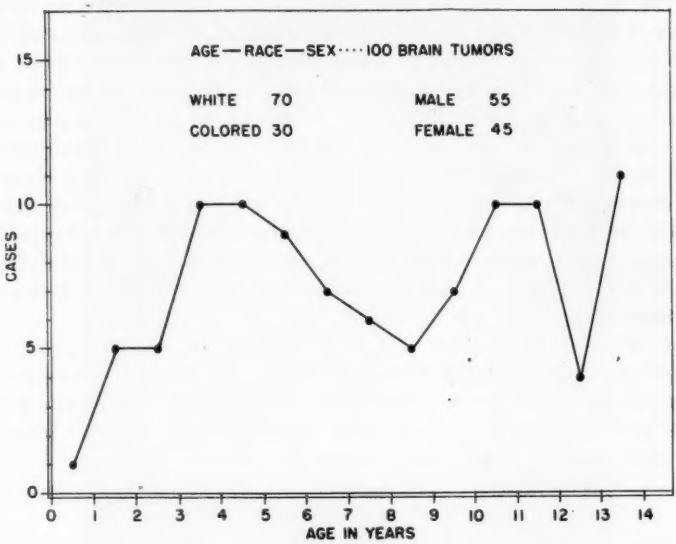

CHART I

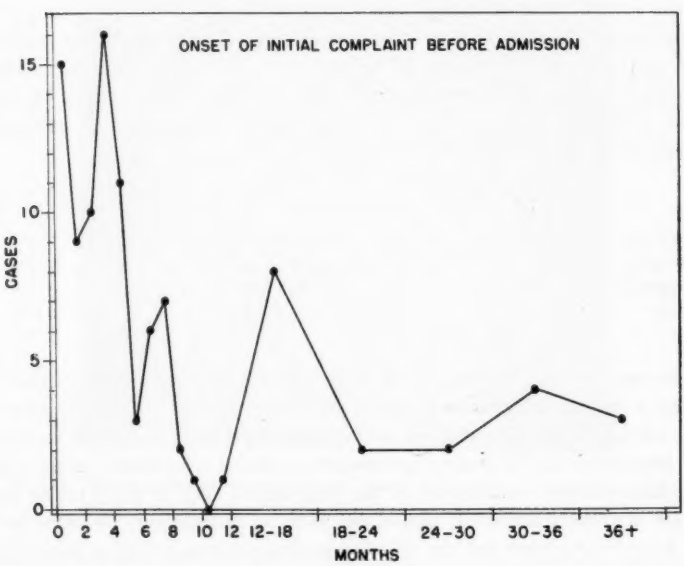

CHART II

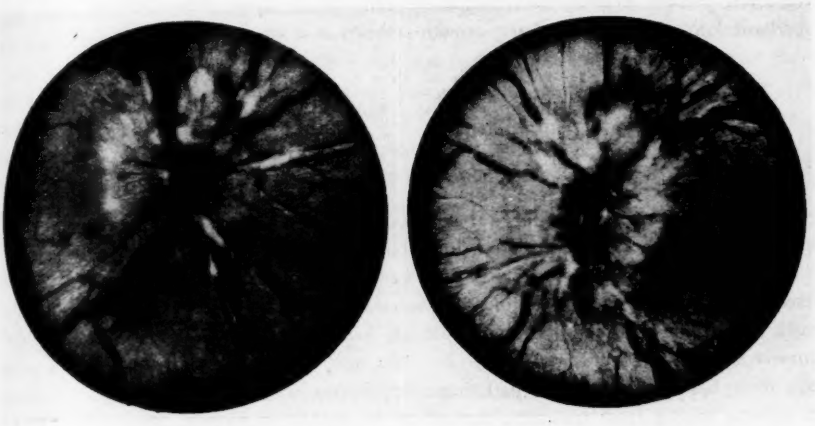

FIG. 6. Bilateral papilledema: in medulloblastoma cerebelli.

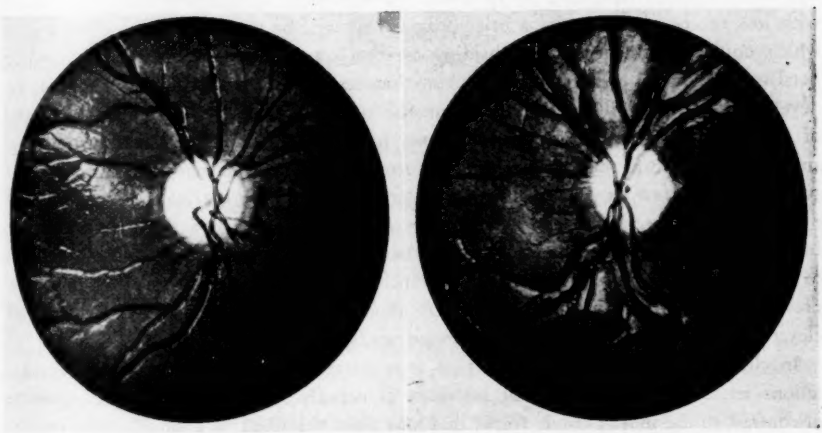

FIG. 7. Bilateral primary optic atrophy in glioma of optic chiasm.

NEUROLOGIC FINDINGS

Ataxia	63%	Enlarged head	21%
Multiple cranial nerve palsies	31%	Cracked-pot sound	28%
Motor paralysis	27%	Cervical rigidity	15%
Signs of increased intracranial pressure		Evidence of increased intracranial pressure in skull X-ray	57%
Papilledema	82%		
Optic atrophy	6%	Abnormal intracranial calcification	6%

As is well known, the practice of pediatric neurosurgery is not a happy one. The vast majority of neoplasms appearing in the age group from birth to 14 years are malignant, either through cell type or because of the location in which they appear. By comparison with other published series, this group of brain tumors in children shows a low number of benign tumors; that is, the cerebellar astrocytomas and the meningiomas.

With our present technical advantages, we can operate upon these children safely but our basic knowledge of neoplastic growth remains at a standstill.

LOCATION OR TYPE OF TUMOR

Pontine	30	Glioma, optic nerve	2
Mid-line cerebellar (medulloblastoma)	27	Craniopharyngioma	2
Cerebellar astrocytoma	11	Meningioma	1
Third ventricle glioma	10	Miscellaneous	17

The third group of neurosurgical conditions in which the recognition of increased intracranial pressure is of paramount importance has to do with the sequelae of trauma.

Another lecture in this series has described one form of chronic intracranial hypertension that may follow head injury, i.e. sub-dural hematoma. The second type of traumatic hematoma, the extra-dural or epidural hematoma, is one in which we all find ourselves committing our most tragic mistakes and, on the other hand, often securing our most happy results. The pathologic lesion consists of an expanding extra-dural hematoma arising from traumatic rupture of the middle meningeal artery or one of its tributaries or veins. The classical clinical picture has been known since 1885, when it was first succinctly described by Jacobson.[6] It consists of a relatively mild head injury, with loss of consciousness for a brief period, followed by the so-called lucid interval in which only the evidence of a subsiding cerebral concussion appears. As the bleeding persists, intracranial pressure increases, consciousness is lost again, contralateral weakness develops and the pupil may be dilated on the side of the hemorrhage. Many variations of the clinical syndrome may exist and we have seen in children not only the acute and dramatic picture, but also delayed syndromes in which characteristic signs of pressure were manifest as late as 10 days after the precipitating trauma. The unilateral dilated pupil is of considerable significance and must be watched for with great care. In all types of head trauma in children, we have found that certain physiologic responses to injury are of some prognostic importance, and in particular the pulse rate. The presence of bradycardia, for instance, has almost always indicated a severe degree of elevated pressure or a severe intrinsic brain injury.

In closing a survey of this subject, it is necessary to mention briefly acute vascular lesions in children that represent instances of rapidly increasing intracranial pressure in contrast to the more chronic forms that have been described. We have become increasingly aware of the fact that spontaneous subarachnoid hemorrhage and intracerebral hemorrhage may occur in children just as they occur in adults and indeed are not uncommon. In these lesions, the rapid rise of intracranial pressure causes loss of consciousness and rather striking changes in pulse, temperature and blood pressure, rather than the symptoms and signs of a more chronic degree of hypertension that have been described. In one patient, acute hemorrhage from a pontine angioma simulated the picture of an extra-dural hemorrhage with a dilated left pupil and a right hemiparesis. In another child, a large subcortical hematoma was associated with a clinically apparent subarachnoid hemorrhage. These childhood lesions have not been studied intensively. However, they are important, stimulating problems, and will prove to be just as difficult to control as the similar vascular lesions of adult life.

Although the title of this discussion has to do with the recognition and treatment of increased intracranial pressure, all reference to treatment has been omitted for several reasons. In the first place, this is not the time to discuss specific neurosurgical methods of

treatment. In the second place, although I am a great admirer of the specialty of pediatrics, I do not feel that pediatrics should embrace the practice of neurosurgery. I feel that lumbar puncture, the use of hypertonic solutions and any form of pediatric appeasement of the presenting problem of increased intracranial pressure represents poor clinical practice. It is equally true however that such measures have a place in the control of critical degrees of intracranial pressure when definitive neurosurgical methods are not immediately accessible. The neurosurgeon is almost completely dependent upon prompt and good pediatric diagnosis of these grave problems of infancy and childhood and only through this division of the tasks of diagnosis and treatment will pediatric neurosurgery progress further.

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Spanish Abstract

El Reconocimiento y Tratamiento de la Crecida Presion Intracraneal en la Infancia y en la Niñez

El reconocimiento de la crecida presión intracraneal en los infantes y niños está influído directamente por dos factores anatómicos: (1) el cráneo es una estructura dilatable con fontanelas abiertas y uniones de huesos maceradas, y (2) el incremento normal del volumen cerebral es atiplado a los tres años de edad y no llega al tamaño adulto sino hasta los 15 años. Por consiguiente, el roentgenograma craneal de un niño en el desarrollo difiere de aquel del adulto y revela la impresión del hemisferio que se ensancha en su superficie interior. La diagnosis radiográfica debe considerar estas variaciones de crecimiento normal y es dependiente de la demostración de un cráneo grande anormal, la atrofia circunvolucional, la separación de los huesos y erosión de la sella turcica. La presión del cerebro que crece normalmente sobre el cráneo queda graficamente demostrada por radiografía en el síndrome del cráneosinostosis; alteraciones patológicas se ven mejor en los estados avanzados de un tumor cerebral.

El estudio de películas radiográficas de 100 pacientes consecutivos con tumores en el cerebro muestran que la presencia de la crecida presión intracraneal se podía sospechar en 63. Una pequeña porción del grupo presentó un corto y casi fulminante acceso de síntomas, y poco más o menos la mitad se quejó de síntomas de crecida presión intracraneal (dolor de cabeza, vómitos, y dificultad visual) y el resto se quejó de síntomas que indicaban un defecto neurológico (bamboleo al caminar, debilidad muscular, etc.). En el exámen neurológico de estos 100 pacientes, 88 mostraron crecida presión intracraneal con sólo el exámen oftalmoscópico. Otras indicaciones patológicas incluían el agrandamiento de la cabeza, un sonido de olla rajada al hacer la percusión del cráneo, y rigidez cervical.

El prognóstico del grupo de esta edad con casos típicos de tumores es favorable solamente en el grupo de astrocítomas celebelares. La seguridad de la intervención quirúrgica en los tumores del grupo de esta edad ha sido aumentada por los adelantos técnicos, sin embargo, nuestra ignorancia acerca del proceso fundamental del tumor aún permanece profunda. El neuro-cirujano depende de la buena y pronta diagnosis del pedíatra.

Duke Hospital

CUP FEEDING OF NEWBORN INFANTS

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THE purpose of this report is to describe an extensive experience over the past 10 years in feeding newborn infants from a cup or glass. The idea of instituting this type of feeding very early in life arose from two observations: 1. Many instances had been encountered in which weaning older babies from the breast or bottle had led to hunger strikes on the part of the baby and the consequent frustration of the mother; and 2. It had been observed that some artificially fed babies had little bodily contact with the mother during the feeding period, since the bottle was simply propped in the crib. There was no way to assure to the artificially fed baby the same pleasurable physical contact with the mother as was enjoyed by the breast fed infant so long as bottle propping was possible. Consequently, for the past 10 years I have employed cup feeding from birth in those babies who were not breast fed, providing that the procedure was agreeable to the parents. This method has also been used to give breast fed babies water, orange juice and other fluids. Parents and nurses using this method of feeding were from all economic and social groups of both urban and rural populations.

The technic for this method is simple. The infant is held securely cradled in his mother's left arm (Fig. 1) similar to the manner used by the mother who feeds her child from the breast. The mother or nurse holds the baby's hands gently in her left hand, so that the baby does not knock the cup or glass aside. The glass is then placed to the lips, over the lower lip and tongue in the normal manner for drinking. (The mother is directed to take a drink of water herself in front of a mirror and then use the same technic in feeding her baby.) Almost immediately when the glass touches the lips the infant will begin to make swallowing movements and regulate the flow of milk into the mouth by mouthing movements involving mainly the lower jaw. The drinking may be somewhat gulping in character, noisy, and a splashing sound is frequently noted. This process continues until the infant pushes the glass from the mouth. Because the baby is held in this upright position, the "burp" is more or less spontaneous. At no time is the infant forced to eat, but is talked to and encouraged by the mother or nurse, attempting to simulate the normal experience of the breast fed infant. The duration of the feeding is short as a rule. The process varies, of course, depending entirely upon the baby, but usually the whole feeding process is completed within five to 10 minutes. With the premature baby, the process is slightly altered. The infant is not removed from the bed, but is raised to a sitting position, supported by the nurse's left hand to the back of the head and the body lies against her left arm.

The necessary equipment for this type of feeding consists of a quart jar or bottle to store the day's supply of milk mixture and a glass. The size of the glass is not of great importance, as the infant will drink from the one-ounce medicine glass or water tumbler; most mothers prefer the fruit-juice glass.

This method of feeding has been successfully employed on full term infants, prema-

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From the Department of Pediatrics, University of Kansas School of Medicine.
(Received for publication June 3, 1948.)

FIG. 1. Method of holding infant for cup feeding.

ture and immature babies, infants with harelip and cleft palate and babies who were healthy and sick. The feeding is started eight to 12 hours after birth. The baby with a harelip or cleft palate consumes his food rapidly and without apparent difficulty, a fact greatly appreciated by the plastic surgeons, since this type of anomaly has always presented a feeding problem. Regurgitation and vomiting seem to occur less frequently when this method is used, and there has been no incidence of aspiration pneumonia. Colic due to aerophagia is practically nil. Sick infants, particularly those suffering from an upper respiratory infection, take their feeding with more ease and more rapidly

from the glass than those depending upon sucking to get their nourishment. The incidence of ear infections has been much lower in cup fed infants with an upper respiratory infection than in bottle or breast fed infants.

There is no question that feeding a newborn infant from a cup is a successful method of meeting the infant's physical needs. Babies who are thus fed gain weight as rapidly as those who are breast or bottle fed. Cup feeding is particularly suitable to the needs of the premature infant and infants with harelips and cleft palates, since many of these infants have minimal sucking capacity. Data on the weight gain of 170 premature infants who were presumably healthy and who were born consecutively at the University of Kansas Medical Center during the past five years are presented in Table I. The average daily weight gain of 111 infants who were completely cup fed from birth is compared to that of 59 premature infants in similar birth weight groups who were fed by other

TABLE I

COMPARISON OF AVERAGE DAILY WEIGHT GAIN OF NEWBORN PREMATURE INFANTS FED COMPLETELY FROM A CUP WITH THOSE WHO WERE FED BY OTHER METHODS

Birth weight (kg.)	Cup Fed			Fed by Other Methods		
	No. of babies	Average days in hospital	Average weight gain (gm./day)	No. of babies	Average days in hospital	Average weight gain (gm./day)
–1.5	8	57	21.5	4	59	19.7
1.5–2.0	41	35	22.2	12	33	17.4
2.0–2.5	62	22	16.7	43	11	9.2

methods. The latter frequently included a combination of breast, bottle, cup and gavage feeding. The weight gains made by the cup fed infants compare very favorably in all weight categories with those made by infants fed by other methods. The selection of the method of feeding employed in this group of 170 premature infants largely was determined by the whim and fancy of the attending physician and the pediatric resident in charge of the nurseries. More of those who were breast fed were Negro infants, since at any given birth weight they were more mature and appeared to have greater sucking capacity. The smallest premature infant who was completely cup fed weighed 860 gm. at birth and was discharged on the 80th day of life weighing 2610 gm.

TABLE II

AVERAGE DAILY WEIGHT GAIN OF 20 INFANTS WITH HARELIP AND CLEFT PALATE UNDER 3½ MONTHS OF AGE

No. of infants	Average days in hospital	Average weight gain gm./day
20	13	22.7

Data on the weight gain of 20 infants under 3½ months of age who were admitted consecutively to the University of Kansas Medical Center during the past year for treatment of harelip and cleft palate are presented in Table II. Nine of the infants had

harelips as their only defect, 10 had both harelips and cleft palates and one had a cleft palate without a harelip. All but the latter infant had cheiloplasties done on an average of four days after admission and remained on an average of nine more days. Their average weight gain was 22.7 gm. a day for the whole hospital stay. All were cup fed throughout.

Discussion

It is recognized that cup feeding instituted at birth, while successful in satisfying the physical needs of the baby, may have important effects on the psychologic behavior of the child. The mechanics of the process calls for less sucking effort than is employed by the bottle and breast fed infant. The question has been raised concerning the effects of a decreased sucking experience in the early months of life on the subsequent behavior of the child, particularly in respect to thumb sucking. It has been implied by some that because these babies have been denied the gratification of sucking in early infancy they would tend to be more frustrated. While no conclusive answer can be given on these points at the present time, the impression has been gained after having watched and cared for several hundred cup fed infants during the past 10 years that the incidence of thumb sucking was no greater in the latter group of babies than in those who were breast or bottle fed from birth. Far from being more frustrated, cup fed babies appeared to adjust to the usual childhood experiences with as great ease as did babies fed by other means. In fact, the introduction of solid foods at three or four months of age seemed to be easier among cup fed infants, possibly because mouthing of a glass or cup was not too dissimilar from taking food from a spoon. Furthermore, the frustrations of the weaning process were entirely eliminated.

The psychologic benefits to the infant of being held in the mother's, father's or nurse's arms during the feeding probably can not be overemphasized. Cup feeding eliminated the impersonal aspect of feeding a baby by propping a bottle in his crib and offered a real opportunity for the parent or nurse to express his or her feeling for the baby during the feeding period. An additional favorable circumstance was the fact that most parents of cup fed babies were agreeable to trying this unusual method, which suggests that they were open minded and possibly more ready to adjust to their babies than most parents. The greatest objections to this method of feeding came from grandmothers who "never heard of such a thing" and to the occasional baby who would not accept the cup or glass.

The personal impressions which have been set forth above have been supplemented by detailed studies at the University of Kansas Medical Center on the comparative behavior of babies and older children who have been fed from the cup, bottle and breast. The results of these studies are in the process of being published.[1,2] Additional studies are in progress.

Cup feeding seems to be particularly suited to the premature and immature infant and to the infant with oral deformities, since swallowing is the only reflex that is necessarily involved. Cup feeding obviates the hazards of gavage feeding of premature infants by the inexperienced attendant. No special skill is required in offering the cup if the occasional spillage is overlooked. Occasionally the spillage is great enough so that considerable calories are lost; this can be made up by offering additional amounts of milk. With practice spillage usually becomes negligible after the first few feedings.

No careful studies have been made of the development of the jaws and teeth of cup fed infants, but no peculiarities have been observed so far in a large group of cup fed infants whose ages range up to 10 years.

Conclusions

A method of feeding the artifically fed infant from a cup starting at birth has been described. Increase in weight is as great when this method is used as in breast or bottle fed infants. Cup feeding is particularly suited to the premature and feeble infant and those with oral defects. The impression has been gained that cup feeding instituted at birth does not lead to psychologic difficulties either in infancy or later childhood. The psychologic benefits of cup feeding have been discussed.

References

1. Davis, H. V., Sears, R. R., Miller, H. C., and Brodbeck, A. S., Effects of cup, bottle and breast feeding on oral activities of newborn infants, Pediatrics **2**:549, 1948.
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Spanish Abstract

Alimentacion de Taza de Niños Recien Nacidos

En los últimos diez años se cuenta con experiencia personal en la alimentación de varias centenas de recien nacidos que han sido alimentados de taza o vaso. El aumento en peso que ha habido en niños prematuros y en niños con defectos en la boca; tales como labio leporino y fisura palatina, indica que este es un método muy satisfactorio para alimentar a estos grupos especiales. Aunque no se pueden citar datos estadísticos, la opinión del autor es que niños de nueve meses no sufren ningún perjuicio psicológico en años subsecuentes como resultado de haber sido privados de la estrenua experiencia de chupar, como la que probablemente acompaña la alimentación de botella o de pecho. Se cree que los infantes que se acostumbran a la taza en una edad muy temprana, evitan las dificultades sensitivas que algunas veces vienen cuando se les comienza a dar alimentos sólidos y al despecharlos.

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EFFECTS OF CUP, BOTTLE AND BREAST FEEDING ON ORAL ACTIVITIES OF NEWBORN INFANTS

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THE psychoanalytic theory that babies possess from birth a libidinal oral drive dominates much of the recent thinking and writing concerned with the emotional development of infants and children. In brief, the theory supposes that the baby not only has a sucking reflex but also a sucking drive, i.e., he gets satisfaction from sucking qua sucking, and wants to suck in the same sense that he wants to eat, evacuate or be warm. The existence of such a drive is inferred from two kinds of behavior. One is the frequent occurrence of non-nutritional or "pleasure" sucking on such objects as the fists, thumbs or bedclothes. The other is the group of frustration reactions (crying, thrashing, further effort) that commonly occur when someone interrupts the non-nutritive sucking.

There can be little doubt that a sucking drive does exist in most infants. Levy[2,3] found that puppies which had little opportunity for vigorous nutritional sucking did more non-nutritional sucking, biting and chewing than puppies that had greater opportunity, and that thumb-sucking in young children was associated with a history of infrequent or interrupted opportunities for sucking during early feeding. But whether the drive that causes such behavior is inborn is difficult to determine. The fact that feeding usually accompanies sucking during the first weeks of life means there is ample opportunity for the baby to learn a sucking drive if he does not already possess it. The necessary conditions for this would be the frequent occurrence of the act (sucking) followed by satisfaction of a primary drive (hunger). To determine whether the sucking drive is inborn or learned requires a comparison of the frequency of oral activities and frustration reactions in two groups of babies, one of which has had the experience of sucking followed by feeding, and the other of which has fed without sucking.

An opportunity to make this comparison was presented to us by a group of babies who were fed from birth from a cup.* This method of feeding reduces nutritive sucking far below that which would occur among babies fed at the breast or from a bottle. According to the psychoanalytic theory, these babies would be expected to show more non-nutritional sucking and more emotional disturbance than babies fed from birth by bottle or breast. According to the learning theory, on the other hand, the cup fed babies should show less indication of a sucking drive than bottle or breast fed babies because they had less opportunity to associate sucking and feeding.

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This study was supported by a grant from Mead Johnson and Company.

(Received for publication June 3, 1948.)

* Cup feeding from birth has been a practice followed by Dr. Robert Fredeen in some babies for several years. Our interest in this study and subsequent ones to be reported derived from his feeling that cup fed babies were not different psychologically from bottle and breast fed children.

The present report is concerned with investigations made on 60 newborn infants divided into three groups of 20 each according to the method of feeding: cup, bottle or breast. Daily measurements were made during the first 10 days of life on the strength of the sucking response, the frequency of non-nutritional oral movements, the amount of general body activity, the amount of crying and the interest in food. The results obtained have been compared for the three groups.

Experimental Conditions

Sixty full term, healthy, newborn infants were used. No infants were included who failed to gain weight as normally expected, who became ill, or who were changed from one method of feeding to another. The decision to place an infant on the breast, bottle or cup was made after prior consultation with the mother and in accordance with her wishes. The bottle and cup fed infants were fed by the nurses in the nursery of the University of Kanasas Medical Center, except that in some instances the mothers took over the feeding on about the sixth day, using the same technic as the nurses. No feedings were given during the first 12 hours following birth; thereafter all infants were fed every four hours. No baby was allowed to feed more than 20 minutes at each feeding. The bottle and cup fed babies were limited to one ounce of milk each feeding on the first day, two ounces on the second day and three ounces thereafter. All artificially fed infants received the same milk mixture, consisting of whole cow's milk to which was added 5% cane sugar and 20% water. Water was offered to all babies ad lib twice a day from the cup, at 10:30 A.M. and 3:00 P.M. Orange juice and cod liver oil were omitted during the experimental period. All infants were weighed before and after feedings at 10:00 A.M. and 2:00, 6:00 and 10:00 P.M. Throughout the study, the breast fed infants nursed a half hour later than the bottle and cup fed babies in order to facilitate the routine of the nursing staff. All observations were made at standard intervals before or after the feedings and not according to the clock.

Feeding methods. The significance of the obtained data, from a theoretical standpoint, rests on the differences between cup feeding and breast or bottle sucking. Cup feeding requires much less time than either of the other methods; although the nurse can govern the duration of cup feeding, the slowest cup feeder ordinarily has oral contact with the cup for a shorter length of time than the fastest bottle feeder, of the same age, has contact with the nipple. Bottle feeding, in turn, is faster than breast feeding. During feeding in the nursery, the cup fed baby is held like a bottle fed baby. He sits upright on the nurse's lap, supported by one hand at the back of his neck. He does not touch or lean against the breast. The cup is put against the lower lip and on top of the tongue, the milk being poured into the mouth as rapidly as the baby swallows. Reflex sucking is often stimulated by this procedure, but usually is considerably diminished, if not completely gone, by the tenth day. The baby's skill at swallowing improves markedly during the first ten days, and therefore the duration of oral stimulation at feeding time decreases daily.

In bottle feeding, the baby has more control over the rate of milk intake and the duration of a meal. Not only the rapidity of his swallowing, but also the strength of his sucking determines how fast the milk is taken. By resting or refusing to suck, he can prolong the period.

Bottle and breast feeding not only provide longer contacts, but the contacts are more

extensive and are associated with vigorous manipulative activity. The cup touches only the lower lip and the tip of the tongue. A bottle nipple stimulates the lips, tongue, gums and palate, and the breast adds cheek and chin stimulation as well. This is of some importance because all these are sensitive areas for eliciting the sucking reflex.

The differences between the three types of feeding may be summarized as follows; in duration of oral stimulation, cup provides shortest, bottle considerable longer, and breast a little longer than bottle; in surface area stimulated, cup is much less than bottle, and breast is a little more than bottle; in vigor of sucking response, cup produces a minimal response that rapidly diminishes, bottle produces an active response that rapidly increases in strength and precision, and breast is similar to bottle except that it involves a more vigorous response because of the greater pressure required to secure milk.

Measurement. Observations were made of five kinds of behavior; (1) the response to a sucking test, (2) spontaneous oral activity, (3) general body activity, (4) crying, and

TABLE I

MEDIAN AND MEAN DURATIONS IN SECONDS OF RESPONSES OBTAINED AT TWO SUCKING TESTS DAILY WITH EACH OF THE THREE GROUPS (20 INFANTS IN EACH GROUP)

Group	Day: Means									
	1	2	3	4	5	6	7	8	9	10
Breast	2.3	5.2	7.0	8.8	7.7	7.5	7.8	5.2	7.0	13.6
Bottle	2.5	6.3	10.1	4.3	6.5	2.2	3.0	6.1	4.4	7.6
Cup	4.0	8.4	5.1	4.7	3.4	8.5	3.4	5.4	5.4	8.7

Group	Day: Medians									
	1	2	3	4	5	6	7	8	9	10
Breast	0	.2	.2	4.0	2.9	7.0	5.2	4.2	5.5	10.0
Bottle	1.1	2.2	5.5	3.0	5.0	1.5	1.0	4.0	2.0	1.5
Cup	1.0	3.4	5.8	2.5	.5	3.5	1.5	1.5	2.0	.6

(5) appetite. The observations were made by two investigators* who practised the various types of measurement together before the study was begun. Each was responsible for the measurements taken at certain hours of the day, and the two sets of data have been combined for statistical analysis. The problem of observer agreement was important only in the observations of spontaneous oral activity and general body activity; the details of the test of agreement will be given below.

Sucking test. The examiner gently inserted his finger, covered with a sterile rubber cot, between the baby's lips and into the mouth. If sucking did not occur within five seconds, a score of zero was recorded. If sucking started within five seconds, the duration of continuous sucking was measured in seconds by a stop watch. Values in Table I refer to "number of seconds."

* Dr. Herbert V. Davis and Miss Margaret Zimmerman, R.N.

The strength of the sucking response, measured by its duration, was tested twice daily. Measurements began two hours after the 6:00 A.M. and 2:00 P.M. feedings. Since there were rarely more than six experimental babies in the nursery at once, the testing required about 15 minutes. This point in the hunger cycle was chosen because the excitability of the response varies positively with degrees of hunger,[6] and it was anticipated that fewer zero scores would be obtained at these times.

Spontaneous oral activity. This was divided into three categories designated as (1) apparent effort to suck, (2) sucking of external object, and (3) intrinsic mouthing. Apparent effort to suck included mouthing movements which were accompanied by head turning and head seeking movements as seen in babies attempting to find the breast or bottle, and mouthing movements accompanied by attempts to bring the hand or some inanimate object to the mouth. Sucking of external object included the actual sucking of the fingers, hands, bedclothes or other objects. Intrinsic mouthing were movements of the lips or tongue unassociated with body movements, such as sucking motions of the lips, protrusion of the tongue, tongue sucking and licking of the lips. A fourth observational category was incidental movements of arms, legs and head. This category was adopted in an attempt to get some measure of general body activity.

Each category was recorded during 10 consecutive periods of 10 seconds each four times a day, one hour before and two hours after the 10:00 A.M. and 2:00 P.M. feedings. The score for each category of oral behavior could, therefore, vary from zero (no movement in any 10-second period) to 10 (movement in every 10-second period). A daily score for each category of oral or incidental behavior could vary from zero to 40. This time-sampling technic has been shown by Olson[5] to give a reliable measure of the total amount of non-nutritional activity.

The morning observations were usually made by one observer and the afternoon ones by the other, although occasionally the observers substituted for one another. On a test series before the investigation was begun, the observers independently but simultaneously recorded the activities of a group of children in the nursery. The agreement between the two records was 90%, i.e., 90% of the entries on the record blanks were identical. Repeated tests of this agreement were made during the investigation itself, and in every instance the agreement was 90% or better for the three categories of oral activity. Agreement on incidental movements was poor toward the end of the investigation.

Crying. A time sampling procedure was used for measuring amount of crying. The babies were observed 30 minutes at a time three times daily, a total of 90 minutes. Each half-hour period was divided into 30 periods of one minute each, and a mark of one was given for any one-minute period in which crying occurred, regardless of volume. The crying score could vary from zero to 90 for each baby in any one day. The time samples of crying were done two hours after the 6:00 A.M. feeding and one hour after the 10:00 A.M. and 2:00 P.M. feedings.

Appetite. To evaluate the babies' enjoyment of their food, judgments of eagerness were made at the 10:00 A.M. and 2:00 P.M. feedings. The two observers practised with other newborns for some days before beginning their judgment of the experimental groups. A scale of three points was defined by the words eager, uninterested or casual, and rejecting. When the observers had agreed between themselves as to what kind of feeding reaction was meant by each of these three terms, they began judging the experimental babies.

Results

Sucking test. The results of the sucking test are shown in Table I. Both the median and mean duration of the response to the sucking test are given, since there were a number of zero scores each day and the distributions were therefore not always symmetrical. In any non-symmetrical distribution of data containing several zero values or a few extremely high values, a median gives a somewhat more stable measure of the group's central tendency than does a mean score. The mean for a given day was calcu-

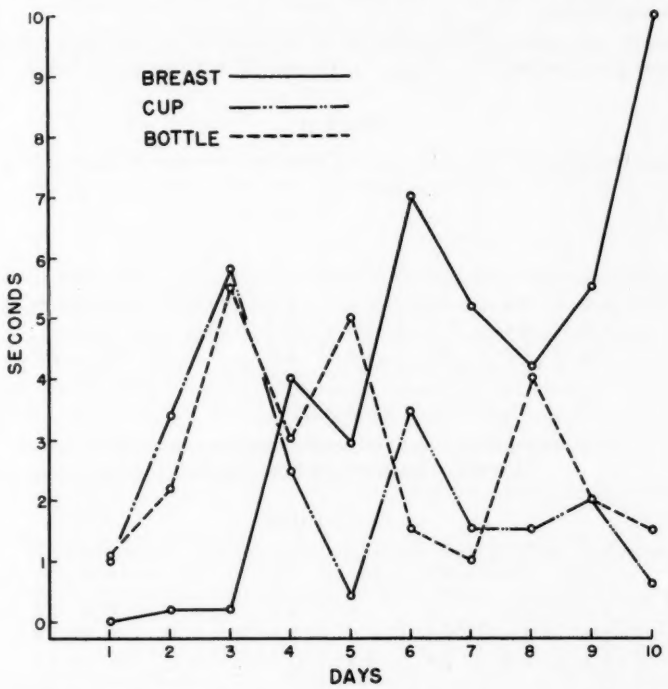

FIG. 1. Median duration of sucking response on first 10 days under three types of feeding.

lated by averaging the two tests for each child and then averaging these values for all the children in the group. The medians were obtained by averaging each child's two tests and then calculating the median of these scores for the whole group.

On only one day was any difference between the means of the three groups significant by a *t*-test. On day 6 the bottle group was unusually low, for unknown reasons, and this mean is different from those for the cup fed and bottle fed groups to a level of confidence of .01.

A comparison of trends in the three groups, however, shows that there was an important difference between the breast fed group and the other two groups (Figure 1). Neither the bottle nor cup fed group showed any significant increase in median duration of response to the sucking test during the ten days. In contrast, the breast fed group,

which started lower than they, increased until it was substantially higher during the last seven days.

This difference in trend is statistically reliable. A *t*-test comparison was made between the average duration for the first three days and for the last seven days. For the first three days, there was not a reliable difference between the groups. For the last seven days, however, the level of confidence between cup and breast groups was $p = < .10$, and between bottle and breast groups, $p = < .01$. The difference between the first three and last seven days for the breast fed group had a reliability of $p = < .10$. None of the other differences were reliable.

Spontaneous oral activity. The results of the observations on the three categories of oral behavior are summarized in Tables II, III and IV.* There was a definite decrease

TABLE II

MEAN FREQUENCY OF 10-SECOND PERIODS CONTAINING APPARENT EFFORTS TO SUCK

Group	Day								
	1	2	3	4	5	6	7	8	9
Breast	2.2	1.4	2.6	2.5	3.2	3.4	1.6	3.1	4.6
Bottle	3.2	2.1	2.4	2.0	3.7	2.6	1.3	2.5	3.2
Cup	2.0	2.0	4.6	2.6	2.0	2.2	2.2	3.0	4.7

TABLE III

MEAN FREQUENCY OF 10-SECOND PERIODS CONTAINING ORAL MOVEMENTS INVOLVING AN EXTRINSIC OBJECT

Group	Day								
	1	2	3	4	5	6	7	8	9
Breast	2.6	1.6	1.6	1.8	1.2	2.0	2.2	1.4	1.8
Bottle	1.9	2.0	1.4	.4	2.2	1.1	.8	.8	1.0
Cup	1.3	1.4	2.6	1.8	.2	1.0	.8	1.5	2.8

TABLE IV

MEAN FREQUENCY OF 10-SECOND PERIODS CONTAINING INTRINSIC MOUTHING MOVEMENTS

Group	Day								
	1	2	3	4	5	6	7	8	9
Breast	11.8	7.5	7.5	6.1	7.5	8.6	6.3	7.4	6.8
Bottle	12.4	8.2	8.4	6.9	7.9	7.2	6.3	7.2	6.6
Cup	12.0	8.8	7.8	5.4	6.9	5.5	6.7	5.6	5.7

* The schedule for releasing babies from the nursery made it impossible to secure complete measures of any behavior except the sucking test on the tenth day. These tables, as well as those for crying and appetite, include data for the first nine days only.

in the intrinsic mouthing movements in all three groups of infants during the first four days (Table IV), but there was no significant change thereafter. There were no significant differences among the three groups of infants in the apparent effort to suck (Table II) or in actual sucking of an extrinsic object (Table III). Both the latter types of oral behavior occurred too infrequently in all three groups of infants to determine whether or not significant differences were present.

TABLE V

MEAN FREQUENCY OF 10-SECOND PERIODS CONTAINING INCIDENTAL BODY MOVEMENTS (GENERAL ACTIVITY)

Group	Day								
	1	2	3	4	5	6	7	8	9
Breast	23.7	21.4	21.2	17.8	20.2	21.9	21.2	23.6	24.0
Bottle	21.4	23.2	21.4	17.9	20.0	16.8	16.5	21.4	19.3
Cup	22.5	19.4	20.8	16.5	17.4	13.3	15.2	19.1	17.9

Incidental movement. The obtained values for incidental movement (general body activity) are shown in Table V. During the first four days, the three groups followed similar patterns, but beginning with the sixth day the amount of incidental movement among the breast fed group was greater. With one exception (the breast-bottle difference on day 8), all the daily differences between the breast fed and the other two groups are statistically significant to the .02 level of confidence, or better, during the last four days. Because of the low agreement on this category, between observers, toward the end of the study, the significance of this trend is questionable.

TABLE VI

MEAN NUMBER OF MINUTES OF CRYING, DURING EACH OF THREE 30-MINUTE OBSERVATION PERIODS, ON THE FIRST FOUR AND LAST FIVE DAYS

Group	Days					
	1–4			5–9		
	8:00 A.M. 2 hr. A.C.	11:00 A.M. 1 hr. A.C.	3:00 P.M. 1 hr. A.C.	8:30 A.M. 2 hr. A.C.	11:00 A.M. 1 hr. A.C.	3:00 P.M. 1 hr. A.C.
Breast	5.4	2.4	3.4	8.4	2.6	3.5
Bottle	5.4	1.8	2.4	8.5	1.7	1.3
Cup	6.1	2.8	1.9	6.5	2.4	2.2

Crying. The results of the time-samples on the crying behavior are shown in Table VI. The behavior was much the same in all three groups. The amount of crying was consistently greater when the time-sampling was done two hours after the feeding, irrespective of the feeding method or the day of life. There appeared to be a general tendency for crying to increase in all three groups as they grow older, but although the breast fed group had slightly higher values than the other two groups during the last five days, none of the intergroup differences was statistically significant.

Appetite. The judgment of appetite showed that there was a significantly greater number of non-eager feedings in the breast fed group than in the other two groups (Table VII). This difference occurred only in the first three days of life.

TABLE VII

FREQUENCY OF NON-EAGER FEEDINGS IN FIRST NINE DAYS; TWO FEEDINGS PER DAY WERE OBSERVED

Group	No. of feedings observed	No. of non-eager feedings	Percent non-eager
Breast	352	47	17%
Bottle	331	31	9%
Cup	343	21	6%

DISCUSSION

Although these three groups of newborn infants had substantially different sucking experiences in food-taking during the first 10 days, few significant differences in the measured forms of behavior were observed. The breast fed group showed a consistent increase in the sucking response to lip stimulation during the first ten days of life, while the response in the other two groups remained unchanged throughout this same period.

Halverson[1] has shown that an infant at the breast needs to exert more physical strength in the sucking process than a baby who is fed from a bottle. It is a well recognized clinical observation that it is usually difficult to get a bottle fed baby to nurse at the breast successfully if the infant has been started on bottle feedings, presumably because of the greater ease with which milk is usually obtained from a bottle. From observations made during the study it was clear that many of the breast fed infants sucked the full 20 minutes allowed, while the bottle and cup fed infants usually consumed their feedings in about half the time. This rewarding of the more vigorous sucking among the breast fed infants, together with the greater number of rewarded sucks they necessarily had, very likely accounts for their increased response to the sucking test (greater habit strength) in the last seven days.

With a stronger response developing, it might be expected that there would be more oral movements of the kind called intrinsic. The reason for this lies in the opportunity for a greater frequency of association of mouth movements with a greater variety of interoceptive and proprioceptive stimuli. The baby should learn to make mouth movements to a greater variety of stimuli. During periods between feedings, these random and nutritionally irrelevant stimuli, as well as hunger drive stimuli, would occur inside the child and then would evoke mouth movements. The data do not support this expectation; the breast fed group did not produce significantly more intrinsic movements.

There were more non-eager feeders in the breast fed group than in the bottle or cup fed groups during the first three days, coinciding with a lesser response to lip stimulation on the sucking test. Breast milk does not flow as freely at first as later and the newborn baby has not developed much skill in getting it. Also, the breast feeding mother is less experienced than the pediatric nurse; the bottle and cup fed babies are approached with more confidence and skill than are the breast fed babies. It is not surprising that the latter infants showed less eagerness.

Parts of the data are relevant to the hypothesis concerning the development of an oral drive. According to the psychoanalytic view, this drive exists as a libidinal component from birth; it is a biologically inherent property of the organism. An alternative hypothesis has been suggested, however; namely, that the oral drive is in part a secondary drive, formed by virtue of the fact that sucking and oral stimulation commonly accompany primary drive reduction of hunger. According to the principles of learning,[4] any act that is instrumental in providing the gratification that comes with reducing one of the basic primary drives, such as hunger, thirst, temperature, regulations, fatigue, etc., becomes gratifying in its own right. A secondary drive is formed, which can be satisfied only by performing this new secondary goal response.

If the first hypothesis is correct (i.e., that the oral drive is native), the cup fed group should show more signs of frustration and more seeking for stimulation than the other two groups. This would follow because the cup fed group got less opportunity at feeding times to satisfy the drive. There is no indication that the cup fed group showed either of these consequences. The breast fed group were more responsive, rather than less, to the sucking test; they did slightly, though not significantly, more crying toward the end of the period; and they showed more appetite disturbance during the first three days. The cup fed group showed less sign of frustration or unsatisfied oral drive than did the breast fed group.

On the other hand, according to the learning theory, the bottle fed babies should have shown behavior similar to that of the breast fed babies. They did not; they were similar to the cup fed group. Possibly this was caused by the use of very pliable nipples that required little vigor in sucking, but this factor was not measured.

The present study does not give any final solution to the problem of whether or not the oral drive is wholly inborn or entirely learned or a resultant of both influences. It does indicate the need for further study and open mind on this problem, on which so much has been written and so little has been done experimentally to evaluate the relevant factors involved.

Summary

Sixty babies were divided into three groups of 20 each, one group being fed by cup, one by bottle and one by breast during the first 10 days of life. The breast fed infants developed a stronger sucking reflex than either of the other two groups, which did not differ from one another. There were no statistically significant differences between the groups with respect to amount of spontaneous oral activity or amount of crying. The breast fed group showed slightly higher general body activity in the last five days and slightly poorer appetite on the first three days.

Acknowledgment

The authors are indebted to Miss Margaret Zimmerman, R.N., for her assistance in making many of the measurements.

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SPANISH ABSTRACT

Efecto de la Alimentacion de Taza, Botella o de Pecho en las Actividades Orales de los Recien Nacidos

Sesenta recien nacidos fueron divididos igualmente en tres grupos, según el método de alimentación usado—pecho, botella o taza, y se estudiaron para ver si había alguna diferencia en el comportamiento oral o general durante los primeros diez días de vida. Las observaciones que se hicieron fueron: (1) cantidad de todos los tipos de comportamiento oral: chupadura de lengua, movimientos de boca, la cantidad del juego oral intentado, incluyendo la vuelta de la cabeza como en busca del pecho, y el esfuerzo de llevarse objetos a la boca, (2) resultado del ensayo de chupadura que consiste en poner un dedo forrado en la boca del infante y medir la duración del esfuerzo de chupar, (3) cantidad de llanto, y (4) interés en el alimento. Todos estos ensayos fueron hechos de una manera standard y en relación al tiempo de comida.

La única diferencia significante que se notó en los tres grupos fué un aumento marcado en la respuesta de los niños de pecho con respecto al ensayo de chupar durante los últimos siete días del período de diez días, comparado con los grupos que toman los alimentos de la taza o la botella. Esta diferencia fué interpretada como una indicación de que el deseo de chupar en los recien nacidos es posiblemente aprendido y se debe simplemente a un proceso innato. Este concepto está basado en el hecho de que los niños a quienes se les da el pecho chupan más fuerte, para obtener el alimento, que los que se alimentan de la botella o la taza, y por eso es que aprenden a chupar más vigorosamente.

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INFECTIOUS CROUP: III. HEMOPHILUS INFLUENZAE TYPE B CROUP

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PREVIOUS reports[1,2] of a study of 347 cases of infectious croup admitted to the Pediatric Service of the New Haven Hospital during the 10 year period 1937 through 1946 presented evidence for the division of this clinical entity into three etiologic categories; namely, diphtheritic croup, so-called "virus" croup, and H. influenzae type B croup. This paper will describe in detail the bacteriology, pathology, clinical course, and treatment of 28 cases of H. influenzae type B croup encountered during the period of the original study. Two case histories will be presented to illustrate the salient differences between H. influenzae type B croup and so-called "virus" croup.

Croup due to H. influenzae type B was first mentioned in the American literature by Alexander in 1940.[3] In 1941 Sinclair[4] described the disease in some detail when he presented 10 cases from this clinic. Since these reports, some confusion has arisen concerning the identity of the etiologic organism.[5] It is different from the usual H. influenzae found in the nose and throat of "healthy" individuals in that it possesses a capsule.[6] This capsule contains a soluble substance which reacts with homologous immune serum and results in capsular swelling (as in the Neufeld technic for typing pneumococci). H. influenzae type B appears to have a definite invasive quality and is the etiologic agent in numerous diseases of childhood.[7] Serologically, it is distinct from the H. influenzae associated with bronchiolitis[8] and, in addition, it has no relation to the Influenza viruses A and B found in cases of epidemic influenza.[9]

The materials and methods used in this study of croup have been described in previous papers.[1,2] This group of 28 cases of infectious croup due to H. influenzae type B includes the original 10 described by Sinclair.[4]

BACTERIOLOGY

H. influenzae type B were recovered from the blood cultures in all but three cases (89.4%). These cases were included in the series because the organism was recovered from the rhinopharynx and the children presented all the other typical features of the syndrome as originally described.[4]

H. influenzae were recovered from the rhinopharynx in 96% of the cases. In 23 cases (85.2%) these were typed and found to be type B.* In each of the remaining five cases H. influenzae type B were found in the blood stream.

Material from the larynx was obtained from three patients. All cultures of this laryngeal material grew H. influenzae. In one instance the organisms were typed and found to be type B. H. influenzae, not typed, were found in both instances in which cultures of aspirated bronchial plugs were made.

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(Received for publication April 1, 1948.)

* In every instance of blood cultures positive for H. influenzae typing was done. Nose and throat cultures were not typed prior to 1941, and this accounts for the finding of H. influenzae, not typed, in the earlier years of the study.

Postmortem cultures of the lung were made from three autopsied cases. H. influenzae type B were found in two cases, and untyped H. influenzae were found in the other.

Cultures from the nose and throat on Löffler's medium were negative for diphtheria bacilli in all cases. Pneumococci of various types were recovered from the rhinopharynx of 11 patients (39.3%). Str. hemolyticus were recovered from the nasopharynx of one case (3.6%). Recovery of staphylococci and green streptococci was noted in all rhinopharyngeal cultures. On the basis of data presented previously[1] the latter two bacteria are regarded as part of the normal rhinopharyngeal flora.

Living Pathology

Laryngoscopy was performed on 15 of the patients. In each case the picture was similar and was characterized by supraglottic edema. A brilliant red, markedly swollen epiglottis was typical of the infection. When this swelling was not such as to obstruct a view of the larynx, the arytenoids and aryepiglottic folds were seen to be similarly involved. Edema and brilliant redness involved the false cords and ventricle often so as to obstruct a view of the true cords. Edema of the true cords and subglottic region was not always present as evidenced by a clear voice in three cases. Pharyngeal and laryngeal membrane was absent on admission in all cases. However, in three patients exudate was noted on the tonsils. In one of these children this exudate developed into a true membrane which later covered the uvula and hypopharynx.

Two of the patients were bronchoscoped during their hospital course. Both showed only slight injection and edema of the lower respiratory tract with crusts patchily covering the mucosa of the trachea and bronchi.

Postmortem Pathology

The postmortem pathology of H. influenzae type B croup is striking. All of the four autopsied cases* died within 20 hours of the onset of croup. Gross examination of the respiratory tract and lungs revealed a marked supraglottic edema and an edematous lung covered with small, brilliant, subpleural hemorrhages. Microscopically the pathologic process appeared to have extended downward in the submucosa of the laryngotracheobronchial tree, possibly by way of the leukocyte-distended lymphatics. The infection resulted in marked degenerative changes in the submucosal glands and the formation of numerous, small submucosal abscesses. The abscesses led to minute ulcerations of the surface epithelium of the epiglottis, larynx and trachea, but not the bronchi. A thin fibrinous exudate covered the epiglottis and larynx. There was extreme congestion of the pulmonary capillaries which culminated in two cases in an outpouring of blood into the alveoli. This was described by one pathologist as a "hemorrhagic pneumonitis." Significant pathologic changes were not noted outside the respiratory tract.

Incidence

These 28 cases of H. influenzae type B croup represented 8.1% of the total cases of infectious croup seen during 10 years' experience. The incidence of the disease by year was sporadic.[2] Seventy-five percent of the cases were admitted during the six months, October through March. The disease was most common in males (68%) and in the

* One of these was admitted to the hospital in 1933 and was included only in this section of the study.

age group from three to seven years (65%). This age incidence was similar to that of diphtheritic croup, but in contrast to so-called "virus" croup as only 21% of the cases occurred in the zero to three year group. None of these patients had a family history of croup, although four (14.3%) of them had had one previous attack of croup which was historically the so-called "virus" type. There was no history of allergy in any of the patients and only 18% of them had a positive family history for allergic manifestation.

Clinical Course

The clinical picture of these cases was characterized by those criteria originally described by Sinclair,[4] i.e., history of a severe sore throat, evidence of laryngitis, fever and leukocytosis, signs of "shock" (severe prostration) out of proportion to the duration of obvious illness and a rapidly progressive course. Certain amplifications are indicated. First, epiglottitis and supraglottic edema are pathognomonic of the disease; second, tender anterior cervical adenopathy is often present; and third, there is a very short duration of obstructive symptoms antedating tracheotomy in those cases requiring operation (8.6 hours, average duration for 13 cases).

History

The history given by such patients is notoriously brief. One-fourth of them had a preceding upper respiratory tract infection, which was mild in all instances. Over half of the patients noted the sudden onset of sore throat severe enough to make swallowing difficult. Within 20 hours these patients were hospitalized. All of the patients suffered a sudden onset of hoarseness or of croup (symptoms of respiratory obstruction). The progress of respiratory obstruction was so rapid that the patients were admitted to the hospital from four to 24 hours following onset, the average duration of the symptom before hospitalization being eight hours. One child died on the way to the hospital, five hours after croup first appeared.

Signs and Symptoms

Typically the children presented severe prostration out of all proportion to the short duration of illness. Occasionally they complained of an extremely sore throat and held their heads in marked extension although no meningeal signs were present. A red, thick, "stiff" epiglottis was seen by laryngoscopy or simple inspection in 80%. In the remaining six cases description of the epiglottis was lacking. All of the patients had marked pharyngitis and in two an exudate was present on the tonsils. Another child developed tonsillar exudate a few hours after admission. One-third of the cases showed a moderate and often tender, bilateral, anterior cervical adenitis. The average temperature on admission was 39°C. The admission WBC averaged 23.1 thousand ($\pm$ 12 thousand). Only one count was under 10 thousand and 50% of the counts were above 20 thousand. There was an accompanying marked polynuclear leukocytosis, the average being 87 ($\pm$ 12) %.

Hospital Course

On the basis of the clinical criteria previously described[1] there were 14 cases of laryngitis, eight cases of laryngotracheitis, and five cases of laryngotracheopneumonitis. As in so-called "virus" croup the duration of the hospital stay and the mortality increased as the disease progressed downward in the respiratory tract. Table I summarizes the principal features of the clinical course of the 27 hospitalized cases.

TABLE I

CLINICAL COURSE OF HOSPITALIZED PATIENTS WITH H. INFLUENZAE TYPE B CROUP

	Duration of hospitalization		Deaths		Duration Temp. over 38° C.	Number tracheotomized	Therapy in surviving patients*					Total Cases
	Surviving cases	Fatal cases	No.	Percent	(days)		SA	ST	SP	SD	A-S	
Laryngitis	11.3 days	1 hour	1	7.1	2.6	7	—	4	1	8	4	14
Laryngotracheitis	16.0 days	3 hours	1	12.5	2.9	1	2	1	—	4	6	8
Laryngotracheopneumonitis	21.0 days	9 hours 2 days	2	40.0	3.4	5 (2)	—	—	1	2	1	5
Average (or total)	14.4 days		4	14.8		13						27†

* Number of patients receiving each type of sulfonamide.

† One case of acute laryngotracheitis was dead on admission, nine hours after the onset of fever and malaise, and five hours after the onset of respiratory obstruction (age 11 years).

SA Sulfanilamide
ST Sulfathiazole
SP Sulfapyridine
SD Sulfadiazine
A-S Type-specific rabbit antiserum
( ) Indicate number of tracheotomized patients who died.

Tracheotomy was frequently resorted to in these patients; one-half of them were subjected to operation. It is interesting to note that 54% of the tracheotomized patients had simple laryngitis (Table I). Following tracheotomy and specific therapy these patients usually showed little improvement until 24 hours had passed. Then the course was one of rapid improvement; there was little difficulty with mucus from the cannula, decannulation was accomplished within a week, and the average case was discharged by the 13th hospital day. Two tracheotomized patients died. Table II summarizes the clinical features of the 13 tracheotomized cases.

TABLE II

SUMMARY OF THE CLINICAL COURSE OF TRACHEOTOMIZED PATIENTS WITH H. INFLUENZAE TYPE B CROUP

Number of cases	13
Percent of total	48.0
Average age	40 months
Range of age	4–84 months
Duration of antecedent illness (URI) (average)	2.7 days
Duration of croup before hospitalization (average)	8.6 hours
Admission temperature (average)	39.0° C.
Admission leukocyte count (average)	
total	24.3 thousand
leukocytes	85%
lymphocytes	13%
Duration of cannulation (average)	6.8 days
Duration of hospital stay (average)	
Surviving patients	13 days
Incidence of positive blood cultures	92.3%
Mortality	15.4%

The course of the non-tracheotomized cases was similar to that of the previous group. Operation did not increase the duration of the hospital stay. Two non-tracheotomized cases died. However, both of the patients were in the hospital less than three hours before death.

Treatment

In treating such patients one is confronted with two problems: first, specific therapy for the toxemia and bacteremia which are the usual accompaniment of the disease; and second, the relief of respiratory obstruction. The paramount consideration is speed.

The method of handling the general problem of respiratory obstruction and the indications for tracheotomy practiced in this clinic have been discussed.[2] One point needs emphasis with respect to croup due to H. influenzae type B. Tracheotomy is the treatment of choice for relieving respiratory obstruction. Intubation is definitely contraindicated because the basic pathology includes supraglottic edema. Since the lip of the tube usually rests upon the glottic chink and is supported by the true cords and ventricle, obstruction of the tube would be brought about by the superiorly located epiglottic edema, providing that it would be feasible to force the tube through the edematous area.

Treatment of the bacteremia and toxemia was carried out with the use of sulfonamides and type-specific rabbit antiserum. On the basis of the "shocked" appearance of the patients, whole blood transfusions have often been given immediately following the establishment of the clinical diagnosis.

Sulfadiazine has been shown to be the drug of choice in treating infections due to H. influenzae type B.[10] Since 1943 this drug has been used exclusively in our clinic in a dosage of 0.2 gm./kg./day, the initial dose being half this amount. Most of the patients were severely ill, and because of this the drug was given by constant intravenous infusion during the first 24 to 48 hours of hospitalization. Sulfadiazine therapy was continued for an average of 8.3 days. Special attention was given to fulfilling the salt and water requirements[11] of the patients because all of them were treated in a steam room.

The decision of whether or not to use type-specific rabbit antiserum in H. influenzae type B croup is a difficult one to make. We have been guided mainly by the clinical appearance of the patient. Of the 27 hospitalized cases, 11 received rabbit antiserum (50-75 mg. of antibody N), two, intravenously and nine, intramuscularly.[12] Each of these patients received a sulfonamide as well and all survived. Twelve other surviving patients received sulfonamide therapy alone. Of the four fatal hospitalized cases, two received a sulfonamide one hour before death. The remaining fatal cases received neither sulfonamide nor rabbit antiserum. Thus, of the twenty-three patients who received a fair trial of specific therapy, none died.

Penicillin was not used in any of these cases because, on theoretical grounds, it was considered to be completely ineffective in this gram-negative bacillary infection.[13] Gordon and Zinnemann[14] have since shown that H. influenzae type B are usually inhibited by 2.5 units of penicillin per cc. of media. However, such a concentration is practically impossible in the blood stream where, in H. influenzae type B croup, the action of an antibacterial agent is most needed. Although streptomycin has been demonstrated to be effective against the etiologic organism,[15] none of the patients in the present study received this antibiotic. Certain theoretic considerations recently published[16,17] cast some doubt upon the advisability of using this antibiotic alone, especially over protracted intervals. However, streptomycin, sulfadiazine, and type-specific rabbit antiserum used early in the

course of the infection is a recommended form of treatment in cases severely ill with H. influenzae type B croup.

Complications

The complications noted in the 23 surviving patients could be divided into two groups, those due to the invasive quality of the bacterium and those due to the mechanical effect of respiratory tract obstruction. Among complications falling in the first group there were three cases of persistent severe sore throat which lasted two days following the onset of treatment. One of these patients had accompanying temporary nasal regurgitation. Another patient who was recovering from H. influenzae type B croup without specific treatment developed H. influenzae type B meningitis. She recovered with type-specific rabbit antiserum and sulfanilamide medication. Two of the patients had crusting of the bronchial and tracheal secretions and one of these died.

In the second group are four patients who developed signs and symptoms of extra-alveolar thoracic air.[18] All of these patients were tracheotomized. It is interesting to note that three of the patients (all of whom survived) developed their symptoms prior to tracheotomy. Two of the children had bilateral subcutaneous emphysema of the neck within four hours after onset of respiratory obstruction. The third child had physical signs of pneumothorax on admission. He was immediately tracheotomized and following this procedure chest X-ray showed mediastinal emphysema and left pneumothorax. The fourth child who died nine hours after tracheotomy was shown to have mediastinal emphysema at autopsy. Thus, 30% of the tracheotomized cases of H. influenzae type B croup showed evidence of thoracic extra-alveolar air.

Analysis of Deaths

The overall mortality in this series was 18%. All of the five fatal cases had an H. influenzae type B bacteremia. In four cases death occurred from nine to 20 hours after the onset of respiratory tract obstruction. The fifth case was a child seen early in our experience who died 48 hours after the onset of croup. He received neither chemotherapy nor antiserum, developed laryngotracheopneumonitis, and died with severe crusting of the bronchi and H. influenzae type B bacteremia.

Three of the fatal cases were not tracheotomized. In two of these death was preceded by a sudden period of marked cyanosis. In the third case cyanosis was gradual in appearance. Another child was tracheotomized but operation only partially relieved the symptoms of respiratory tract obstruction. Nine hours later the child died. Autopsy showed mediastinal emphysema and an edematous laryngotracheobronchial mucosa. The second tracheotomized fatal case had severe crusting of the bronchi unrelieved by repeated bronchoscopy.

It thus appears that obstructive anoxia played a part in each of the five fatalities, although one must not forget that bacteremia and toxemia were also present. These patients emphasize the necessity for early tracheotomy in selected cases and prompt chemotherapy in every case as treatment par excellence of this fulminating infection.

Case Reports

The following case histories are presented to summarize the differences between the clinical course and treatment of so-called "virus" croup[2] and croup due to H. influenzae type B. Both patients were admitted to the hospital with the chief complaint of "croup."

J. P., a 2½-year-old white male with a negative past and family history, had a mild upper respiratory tract infection. This continued for one week when within an hour he became hoarse and had respiratory difficulty. This progressed rapidly and five hours later he was admitted to the New Haven Hospital. On admission, temperature was 39.0° C. He was pale-grey and in shock. He had marked inspiratory and expiratory stridor and was retracting severely. Moderate rhinitis and pharyngitis were apparent. Hoarseness was present. Epiglottis was easily visible, and was purple-red and swollen. WBC was 12 thousand, differential count showing 92% leukocytes, 6% lymphocytes. Culture of the rhinopharynx revealed Pneumococcus VI and H. influenzae type B. Blood culture was positive for H. influenzae type B. The child was treated immediately with constant steam and intravenous sulfadiazine. The respiratory obstruction was not improving, and one-half hour after admission a tracheotomy was done. Following this a whole blood transfusion was given, and a constant infusion was kept running for the ensuing two days. Sulfadiazine was continued for nine days, intravenously, by clysis, and subsequently by mouth. He improved gradually and the temperature fell to normal limits on the second day. He was decannulated on the fourth day, and taken out of steam on the fifth day. He was discharged from the hospital on the twelfth day following admission. Follow-up examination one week later was negative.

J. B., a two-year-old white male, was admitted to the New Haven Hospital. "Colds" had been present in both parents and one sibling for the previous week. One year previously the patient had had his first attack of croup which was treated at home. Two days prior to admission he developed symptoms of a mild upper respiratory tract infection. The next day he exhibited hoarseness and a barking cough. That night symptoms of moderate upper respiratory tract obstruction appeared and progressed slowly during the following day when hospitalization was advised. On admission temperature was 37.8° C., and he looked only moderately and acutely ill. He had a hoarse voice, barking cough, slight inspiratory crow, and moderate inspiratory retraction. Examination revealed a mild rhinitis and pharyngitis. WBC was 12 thousand, 63% leukocytes, and 30% lymphocytes. Cultures of the rhinopharynx grew Pneumococcus VI. Blood culture was sterile. The child was placed in the steam room and oral sulfadiazine was given. This was continued for three days. The temperature returned to normal by the second hospital day and hoarseness and obstructive symptoms were gone within the same interval. He was in steam three days, and was discharged from the hospital in five days.

The tempo of these two cases is very different. The severe prostration, polynuclear leukocytosis, epiglottitis, rapidly progressive course, and bacteremia seen in the first patient were absent from the second. The first case was obviously one of H. influenzae type B laryngitis with bacteremia, while the second case was one of so-called "virus" laryngitis.

Summary

Croup due to H. influenzae type B occurred in 8% of a group of 347 cases of infectious croup. Bacteriologically and pathologically the disease was distinct from diphtheritic and so-called "virus" croup.

Clinically this form of croup is characterized by the extreme rapidity of onset and the severity of symptoms. The outstanding clinical signs and symptoms encountered were: severe sore throat, epiglottitis with supraglottic edema, extreme early prostration, marked leukocytosis with a high polynuclear percentage, tender anterior cervical adenitis, and necessity for very early tracheotomy in selected cases.

Treatment consists of two important parts: relief of respiratory obstruction and treatment of the accompanying bacteremia and toxemia. The former calls for early tracheotomy to avoid the frequent adverse results of thoracic extra-alveolar air; intubation is contraindicated. Treatment of the second problem calls for transfusions of whole blood plus early administration of type-specific rabbit antiserum and sulfadiazine and streptomycin in high dosage.

Death from H. influenzae type B croup is attributed to bacteremia and toxemia, aided by progressive respiratory tract obstruction.

ACKNOWLEDGEMENTS

The author wishes to acknowledge the valuable advice and criticism given him in the preparation of this paper by Dr. Grover F. Powers, Dr. Paul L. Boisvert and Dr. Donal L. Dunphy.

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SPANISH ABSTRACT

Crup Infeccioso. III. Crup Hemofilus Influenza Tipo B

El crup debido al H. Influenza tipo B, ocurrió en 8% de un grupo de 347 casos de crup infeccioso. Bacteriologica y patologicamente, la enfermedad fué distinta del crup diftérico y del llamado crup "virus." La imagen endoscopica fué de extrema inflamación supraglótica y epiglotis. Clinicamente la enfermedad se caracterizó por lo siguiente: historia de breve antecedente de dolor de garganta intenso, comienzo súbito, sintomas rápidos y progresivos de crup, adenitis cervical blanda, evidente laringitis y marcada epiglotitis, leucocitosis y signos de shock desproporcionados con la duración de la enfermedad. El tratamiento consistió de dos partes: 1. mejorar la obstrucción supraglótica por traqueotomía, y 2. combatir la bacteriemia y toxemia con sulfamidas, antisuero de conejo de tipo específico, y transfusiones. La muerte por esta enfermedad fué atribuida a bacteriemia y toxemia, ayudadas por obstrucción progresiva del tracto respiratorio. El total de casos fatales por esta forma de crup fué de 18%, siendo 7% por laringitis y 40% por laringotraqueoneumonitis.

789 Howard Ave.

URINARY RETENTION DUE TO HEMATOCOLPOMETRA

Report of Two Cases—One with Spontaneous Recovery

By ALLAN BLOXSOM, M.D., AND NORBORNE POWELL, M.D.
Houston, Texas

HEMATOCOLPOMETRA may be one of the extrinsic causes of acute urinary retention in the female. It can eventuate in spontaneous recovery due to rupture of the hymen with results which are both startling and comforting to the patient. Occasionally there is associated a partial intrinsic narrowing of the urethra.

CASE REPORTS

Case 1. E.F.S. (AE 8989 Jefferson Davis Hospital), a 13-year-old Negro female, reported through the courtesy of Dr. Marvin Rape, was seen in the accident room for treatment. She was in acute distress and gave a history of not urinating for 24 hours. There was considerable pain throughout the abdomen. Family history was essentially normal and she had had no operations. There had been menstrual molimina but no menarche.

Physical examination revealed a distended bladder about half way above the symphysis. A #16 olive tip catheter was inserted easily into the bladder and it was emptied of approximately 500 cc. of clear, concentrated urine. Urinalysis was normal.

There was a bulging mass in the vaginal orifice which was tender to pressure. Under novocaine anesthesia the intact hymen was incised and 1000 cc. of thick chocolate-colored menstrual fluid was evacuated with immediate relief of the abdominal discomfort. Palpation revealed both tubes and ovaries normal and uterus normal, though displaced upward and posteriorly.

One week later the patient returned to the clinic and examination revealed pelvic organs in normal position. The patient at this time stated that she had had no difficulty in voiding and no further discomfort in her abdomen. She had some bloody vaginal discharge for several days after the evacuation of the hematocolpos. She has not returned to the clinic since and it is presumed that she has been permanently relieved of her urinary difficulty.

Case 2. C.E.E., a white female, age 12 years 3 months, was seen in the emergency room at St. Joseph's Hospital, giving a history of swelling in her abdomen for a week and not voiding for 12 hours. The mother stated that she had noticed that the child had been rather full in her abdomen for several months, but she thought the immediate present difficulty dated back about a week. At that time the child had had some difficulty in voiding and complained that she felt that her bowels had to move. This feeling was never entirely relieved. There was no menarche or symptoms suggestive of the menarche.

Physical examination showed the girl to be in considerable distress. Perspiration was noticed on her forehead and she held herself doubled up. There was a large mass in the lower abdomen, about seven inches in diameter. This mass was smooth, extended about 5 cm. above the symphysis and was somewhat tender. The vaginal orifice was occluded by a bulging mass.

She was sent to the X-ray room for roentgenograms of the mass in the abdomen. After two films were made (Fig. 1), she was asked to sit up in order to get off the table. As she did so there was a sudden release of about a gallon of a bloody chocolate-colored fluid. An additional plate of the abdomen was made and the mass had completely disappeared.

She was sent home with the advice to report in two days for an urologic examination. Both breasts were developed. The abdomen showed no tenderness and there was no discomfort in either costovertebral angle. On deep pressure over the symphysis there was some discomfort.

There was a reddish-colored bulging mass in the vaginal orifice which was tender to the touch.

From the Department of Urology, Baylor University College of Medicine.
(Received for publication June 14, 1948.)

On bimanual palpation about one ounce of fluid could be felt in the region of the vagina and by pressure per rectum a thin trickle of menstrual fluid was expelled through a tiny rent in the hymen.

There was a tight urethra, which was dilated to a #22 F.S. before a #20 McCarthy penendoscope was introduced. The bladder was normal. The urethra showed some polypoid granulations in the posterior part, and at six o'clock (posteriorly) there was a definite suburethral intrusion into the urethra. It is easy to see how distention of the vagina with the menstrual fluid would have occluded

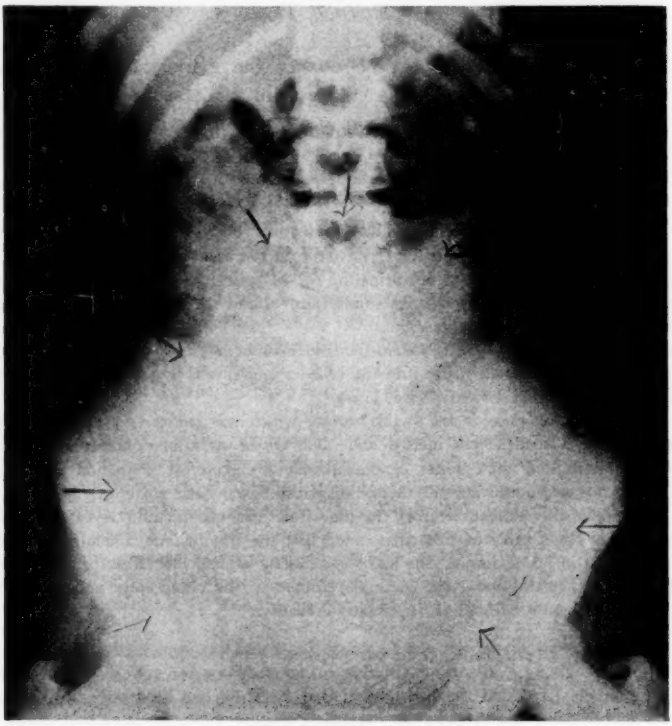

FIG. 1

completely this narrowed, slightly obstructed bladder neck and urethra. The hymenal rent was easily enlarged by forceps.

Roentgenograms during intravenous pyelography showed the kidneys, ureters, and bladder to be of normal size, outline and position. Both kidneys excreted the dye well. There was a slight dilation of the minor calices of the left kidney.

COMMENT

Acute complete urinary retention due to hematocolpometra as compared to bladder disfunction is a rather rare urological condition complicating hematocolpometra as evidenced from the fact that only seven cases have been reported. Snodgrass[1] in 1931 first reported such complete urinary retention in a 14-year-old girl. No mention was made of any urethral abnormality being present. Lazarus[2] reported two cases, both in 12-year-old girls. In both of Lazarus' cases there was an obstruction at the vesical neck of the

bladder. The retained blood in the vagina associated with the obstruction at the vesical neck with further angulation as the result of the forward pressure of the blood-filled uterus upon the posterior wall of the bladder resulted in the acute urinary retention. The fourth case was described by Mouradian.[3] No mention was made of any intrinsic urethral narrowing. The fifth case reported in the literature was by Tompkins[4] in 1939. No mention was made of any intrinsic urethral narrowing. The sixth case reported was by Lacal,[5] and the seventh by Flax.[6]

In both of Lazarus' cases and in one of the cases reported here there was a slight obstruction of the urethra made complete by the accumulation of menstrual fluid in the vagina. Relief through spontaneous rupture of the hymen has occurred only in the one case reported here.

Summary

Two additional cases of acute urinary retention due to hematocolpometra have been added to the seven cases already reported.

In three of the nine cases reported there has been a partial, congenital, intrinsic obstruction of the urethra which together with the extrinsic hematocolpometra resulted in the complete bladder obstruction.

Spontaneous rupture of the overstretched hymen can occur; and, when it does, it leads to relief and recovery.

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Spanish Abstract

Retencion Urinaria Debida Al Hematocolpometra. Informe de dos Casos—Uno Con Restablecimiento Espontaneo

Se ha sabido de dos casos de completa retención urinaria aguda debida al hematocolpometra. En un caso hubo alivio espontáneo debido a que el himen se fracturó cuando la paciente se sentó en la mesa de exámen. Han habido siete casos anteriores en la literatura además de los dos mencionados aquí, y se cree que tres de los nueve casos han tenido un estrechamiento congénito intrínsico de la uretra.

4402 Travis St.

IMMUNOLOGIC AND BIOCHEMICAL STUDIES IN INFANTS AND CHILDREN WITH SPECIAL REFERENCE TO RHEUMATIC FEVER

V. Electrophoretic Patterns in Blood Plasma and Serum in Normal Children

By ROSE LUBSCHEZ
New York, N.Y.

STUDIES of the electrophoretic patterns of sera of various animals have revealed that different species have a characteristic and reproducible pattern. The number and relative quantity of the various protein components were found to vary significantly with the species, but no significant differences were observed in several animals of a given species.[1,2] No data have been presented to indicate that within an animal species, genetic differences produce variation in the characteristic pattern, although this possibility might be considered. In man, the pattern for normal adults has been found to be remarkably constant. Few data have been reported for children.[3,8]

Changes in the electrophoretic pattern due to age have been considered. It has been found that newborn infants have an abnormally high gamma globulin component, which correlates with the natural immunity of this age group.[4] Before the ingestion of colostrum, newborn calves were found to have no significant amounts of gamma or beta globulin. Both of these components increased well beyond normal limits in the first five days of nursing, and were reduced to normal limits by one year of age.[5] It has also been observed that in young children, the percentage of albumen is higher, and with increasing age this value gradually decreases to adult levels.

No studies have reported that there is a sex difference in electrophoretic patterns of human sera.

The most marked changes in the electrophoretic pattern occur during disease. Decreased albumen levels have been observed in malnutrition, kidney disease and, to a lesser degree, whenever the globulin values are elevated in serum in which the total protein content is normal. The alpha globulin levels are elevated in a variety of conditions, all of which are associated with an inflammatory reaction. An increase in the beta globulin component has been associated with liver damage. The significance of minor variations in the fibrinogen level is unknown. Elevation of the gamma component occurs during or following infectious diseases. The relation of antecedent illness to changes in the various components has not been evaluated in the description of the normal pattern.

The present investigation is concerned with electrophoretic patterns in normal children in apparent health. The possible influences of heredity, age, sex, and antecedent illness are considered.

From the New York Hospital and the Department of Pediatrics, Cornell University Medical College.

This study was aided by a grant from the Commonwealth Fund.

The advice and constructive criticisms of Dr. Theodore Shedlovsky are gratefully acknowledged.

(Received for publication June 8, 1948.)

Material and Methods

Material: For electrophoretic analysis, blood specimens were taken from 59 children over a two year period. The children ranged in age from under one year to eleven years, with a mean age of 5.0 years. There were 24 boys and 35 girls. These children were under continuous medical supervision in the Children's Clinic of the New York Hospital as part of a genetic study. Each child was seen in the clinic at least four times a year, home visits were made during illness, and a careful history of illness between clinic and home visits was taken. Of this group of 59 normal, non-rheumatic children, seven came from families in which both parents were rheumatic, and 28 came from families in which one parent and several close relatives were rheumatic.

Method: The plasma or serum which was obtained over a two year period was stored in sealed pyrex tubes under sterile conditions in a refrigerator whose average temperature was $-20°C$. The specimens varied in volume from 3.0 to 4.5 ml. For the larger specimens, one volume of serum or plasma was diluted with two volumes of buffer to make a final volume of 12 ml. or more. Smaller samples were diluted with sufficient buffer to make a final volume of 12 ml. Barbiturate buffer was used for all determinations (0.1 N NaV, 0.02 N HV, pH 8.60, ionic strength 0.1). Diluted specimens were dialysed in Visking casing against two liters of buffer for three days at 2-6°C. Electrophoresis was carried out in the Tiselius-Longsworth apparatus.[6]* The patterns were photographed, and projections (2.5x) were traced on bond paper. The area enclosed by the base line and the protein peaks was measured with a planimeter, and the areas under the various peaks were measured. Equating the total area to 100%, the relative concentrations of the various components were calculated. The average values of the ascending and descending boundaries were used. The total protein concentration of the samples was measured in a kerosene-brombenzene gradient tube.[7]

All electrophoretic determinations were made using a current strength of 15 ± 0.2 milliamperes which was applied for sufficient time to obtain resolution of the components, the time varying from 100 to 150 minutes. Conductivity of the specimen and buffer was determined, and these values were used to calculate the mobilities of the various components.

For the entire procedure, it was found that duplicate determinations on the same sample could be reproduced within 3%.

Results

In Table I, the electrophoretic analyses of blood specimens from 30 children in apparent health are presented. The children ranged in age from two to 11 years, with a mean age of 5.8 years. There was no record of any illness in this group for a period of at least four months and as great as one year in some instances. The mean values for the relative concentration of the various components are shown to be in close agreement with those obtained by Dole for a series of 15 healthy young male adults.[8] However, from the calculated standard deviations, it will be observed that the greatest variation occurs in the albumen and gamma globulin peaks, and that this variation is several times greater than that obtained by Dole. The total serum or plasma protein levels were within normal limits in this group.

* The cooperation of the Department of Biochemistry in making the apparatus available to us, and providing technical assistance is gratefully acknowledged.

TABLE I

ELECTROPHORETIC DATA FOR NORMAL CHILDREN WITHOUT ANTECEDENT INFECTION

Age	No.	Sex	A	α_1	α_2	β	ϕ	γ
2	208	F	61.6	3.6	8.3	20.4	—	6.1
2	33	F	62.2	5.3	11.1	12.4	2.6	6.2
2	74	M	61.0	4.6	8.9	15.7	4.5	5.2
3	117	M	69.7	2.6	8.7	12.2	1.5	5.3
3	121	M	59.8	3.7	9.2	13.7	6.2	7.3
3	345	F	60.4	4.2	9.8	17.0	—	8.5
3	58	F	59.0	6.3	7.4	11.7	4.4	11.2
4	344	F	64.4	5.3	9.4	11.5	—	9.4
4	104	M	62.1	4.9	8.9	14.0	4.5	5.5
2–4			62.2	4.5	9.1	14.3	4.0	7.2
5	212	M	40.7	7.7	12.9	15.5	6.3	16.9
5	37	M	54.9	3.9	11.7	12.4	6.1	11.3
5	437	M	54.3	7.7	14.9	9.7	—	13.2
5	34	M	62.8	2.9	7.8	11.5	3.9	10.9
6	148	F	54.1	5.1	10.9	11.9	6.8	10.9
6	178	M	60.3	5.0	9.8	12.0	7.2	5.6
6	98	F	70.6	3.6	7.8	8.1	1.9	7.9
6	78	M	50.0	6.7	11.1	11.9	7.2	12.9
6	181	F	69.0	3.7	6.7	13.4	3.2	3.9
6	83	M	61.1	4.0	10.4	12.9	5.9	5.8
6	103	M	48.8	5.8	10.8	13.0	7.9	13.6
7	86	F	62.3	2.7	7.9	12.6	5.3	9.2
7	18	F	49.1	8.1	6.3	14.4	8.2	14.0
7	82	F	53.9	6.7	8.2	10.3	5.7	15.0
7	120	M	55.9	5.1	7.7	13.1	4.6	14.1
5–7			56.5	5.2	9.7	12.2	5.7	11.0
8	31	F	55.3	4.9	8.9	10.2	6.1	14.4
8	179	M	72.9	2.8	13.7	3.4	3.0	4.2
9	80	F	56.7	3.9	11.0	13.0	5.0	10.4
10	141	F	58.0	5.6	10.0	11.8	5.0	9.4
11	66	M	58.7	5.8	9.0	13.3	5.0	6.8
11	140	F	54.1	5.3	6.1	15.9	8.8	9.4
8–11			59.3	4.7	9.8	11.3	5.5	9.1
Mean: 5.8.			58.8	4.9	9.5	12.6	5.3	9.5
Standard Deviation			6.9	1.5	2.0	2.9	1.8	3.6

No significant difference in the relative concentration of the various components was observed between girls and boys. There is a slight trend in favor of higher albumen levels and lower gamma globulin levels in the age group two to four years, in comparison to the age groups five to seven years and eight to 11 years, but the range in

levels within each age group is approximately the same. All of these variations are well below the limits of statistical significance.

Two determinations made on children under one year of age fell within the normal limits of this series, suggesting that over the age of six months, the levels in normal children do not differ significantly from adult levels. It is interesting to note, however, that one of these children, who had not received routine prophylactic immunizations had a gamma globulin level of 4.7%, in contrast to the other, whose gamma globulin level was 13.6% within one month of routine prophylaxis.

TABLE II

SUMMARY OF ELECTROPHORETIC DATA FOR 27 PATIENTS WITH ANTECEDENT ILLNESS

	Mean age	A	α_1	α_2	β	ϕ	γ
Range in normal values	5.8	45.0–72.8	1.9–7.9	5.5–13.5	4.8–20.4	1.7–8.9	2.3–16.7
Mean values for patients with antecedent illness	4.6	50.9	6.5	11.5	12.8	6.2	15.5
Number of abnormalities found*		5	5	5	—	1	12

* An abnormal level was considered to be more than twice the standard deviation for mean normal values.

In Table II, the mean values for a group of 27 children in apparent health but who had been sick within four months are presented.* The mean age of this group was 4.6 years. The antecedent infections included tonsillitis, known streptococcal infections. sore throats, otitis media, cervical adenitis, childhood diseases (rubeola pertussis, epidemic parotitis, varicella, rubella, scarlet fever), Perthe's disease, bronchopneumonia, and peritonsillar abscess. While the mean value for the beta globulin component is unchanged, the other components differ from the previous series by about one standard deviation, representing a decrease in the albumen level, and an elevation of the remaining globulin levels. The number of determinations which fell beyond normal limits (twice the standard deviation) are listed for each component. It is noteworthy that in a series of 27 normal children, several abnormal values were observed for each component except beta globulin. The number of elevated gamma globulins is significantly greater than this, since about 44% of the determinations revealed gamma globulin levels above 16.7%. The serum protein levels were within normal limits for all of these subjects.

An attempt was made to correlate the interval since illness with the levels of the various components. In Table III, the number of patterns with abnormal concentrations of at least one component are presented in relation to the interval since illness. It may be observed that abnormalities occurred in one specimen three months after recovery from an illness, although illness within one month produced the greatest number of variations in the normal pattern.

* Three children had not recovered completely at the time the specimen was taken.

The patterns of seven children both of whose parents were rheumatic were given further consideration to determine the possible effect of hereditary susceptibility to rheumatic fever. Six of these children were in the well group, and had normal patterns. One child was in the sick group and had elevated alpha 1 and alpha 2 peaks three months following tonsillitis and otitis media. It is apparent that these children do not differ in response or serum protein pattern from children who are not susceptible to rheumatic fever on a genetic basis.

TABLE III

ABNORMALITIES FOUND AT VARIOUS INTERVALS SINCE ANTECEDENT ILLNESS

Well interval	Total no. of determinations	No. of determinations with at least one abnormal finding	Number of abnormalities found					
			A	α_1	α_2	β	ϕ	γ
Less than 1 month*	17	12	5	3	4	—	1	11
1 Month	3	2	—	1	—	—	—	1
2 Months	4	—	—	—	—	—	—	—
3 Months	3	1	—	1	1	—	—	—
Total	27	15	5	5	5	—	1	12

* Includes three patients who were not completely recovered at time specimen was taken.

DISCUSSION

An attempt has been made to establish normal values for electrophoretic patterns in children. Since children are affected by illness more frequently than adults, and because abnormalities may persist for several months after illness, it was necessary to exclude those known to have had an infection prior to the time the blood was taken. Although the mean values obtained agreed within experimental error with the values obtained by Dole for adults, the variation for each component was greater, particularly in the albumen and gamma globulin fractions. Part of this variation may be attributed to differences in the final concentration of protein in the specimens analyzed. This could not be avoided because only limited amounts of blood could be obtained from some of the children. Perlmann and Kaufman have shown that at lower concentrations of protein, the percentage of albumen tends to be lower.[9] Since increases in the gamma component are due in some part to antibody production, the greater variation observed in normal childhood values might be expected.

From the results on the group with antecedent infection, it is apparent that infection will produce abnormalities in the pattern which may persist over a period of several months. Although every effort was made to record the occurrence of each illness there was probably some over-lapping between the two groups which were considered to be with and without antecedent illness. The observation that more than one third of the determinations made on children who had suffered some type of infection within one to four months showed an elevated gamma globulin component is significant. It is also of interest that there was some correlation between pattern abnormalities and the

duration and severity of the illness. An illness of several weeks' duration will produce more extensive abnormalities in the pattern than one of a few days, unless the latter is very severe. Repeated minor infections over a period of time appeared to build up the gamma globulin level.

Serum protein levels of all of the children in this study were within normal limits. The variations which were observed in both groups could not be attributed in any instance to hypoproteinemia.

Since this was a comparative analysis of known protein components, it was not necessary to determine the mobilities of the various fractions. The data were available for analysis, however, and it was found that the mobilities of the various components agreed within experimental error with Dole's values for adults.

A sex difference in the electrophoretic pattern was not expected and was not found. The breakdown by age confirmed the observation that the albumen level is slightly higher in younger children and that the gamma globulin component is slightly lower. The small increase in the normal gamma globulin level with increasing age may reflect the gradual production of antibodies during childhood.

Summary

Electrophoretic analyses of blood plasma or serum of 30 children in apparent health between the ages of two and 11 years revealed that the relative concentration of the various components was in close agreement with adult values, although the individual variation was several times greater.

For 27 children in apparent health, but who had experienced various types of infection during a one to four month interval prior to the time the specimen was taken, elevation of the gamma component occurred in about 40% of the determinations. Illness within the month produced the greatest number of abnormalities, although abnormalities were noted in specimens of children who had been free of infection two to three months. A few abnormalities were noted in all components except beta globulin.

At younger ages (two to four years) children showed a slightly higher albumen level and a slightly lower gamma globulin level.

Normal children susceptible to rheumatic fever on a genetic basis exhibited no specific differences in the electrophoretic pattern.

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SPANISH ABSTRACT

Estudios Inmunologicos y Bioquimicos en Infantes y Niños con Referencia Especial a la Fiebre Reumatica. V. Modelos Electroforeticos en el Plasma Sanguinea y el Suero en Niños normales

Fueron determinados modelos electroforéticos en el plasma sanguíneo y en el suero de 59 niños normales de uno a once años de edad en aparente buena salud. Se tomaron en consideración posibles influencias de herencia, edad, sexo y enfermedades anteriores. Las determinaciones fueron hechas por el método publicado en el aparato Tiselius-Longsworth, usando un regulador barbitúrico.

Los análisis de plasma sanguíneo y de suero de 30 niños de dos a once años de edad, en aparente salud, revelaron que la concentración relativa de los varios componentes concordaban estrechamente con los valores adultos, aunque la variación individual era muchas veces mayor.

En 27 niños en aparente salud, pero quienes habían tenido varios tipos de infección durante un intervalo de uno a cuatro meses antes de tomarse la muestra, la elevación del componente de gama ocurrió en un 40% de las determinaciones. La enfermedad durante el mes produjo el mayor número de anormalidades, aunque también se notaron anormalidades en muestras tomadas de niños que habían estado libre de infección de dos a tres meses. Se notaron unas pocas anormalidades en todos los componentes con excepción de la beta-globulina.

En edades tempranas (dos a cuatro años) los niños mostraron una nivelación de albumen un poco más alta y una nivelación de gama-globulina un poco más baja.

Los niños normales susceptibles a fiebre reumática en una base genética no mostraron diferencias específicas en el modelo electroforético.

525 E. 68th St.

IMMUNOLOGIC AND BIOCHEMICAL STUDIES IN INFANTS AND CHILDREN WITH SPECIAL REFERENCE TO RHEUMATIC FEVER

VI. Electrophoretic Patterns of Blood Plasma and Serum in Rheumatic Children

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THE changes in the electrophoretic pattern of blood plasma and serum have been correlated with various abnormal conditions.[1] In pneumonia, scarlet fever, rheumatoid arthritis and rheumatic fever, an increase in the gamma component is considered to reflect in some measure, the response of the host to infection.[2-7]

In rheumatic fever the observed increase in the gamma globulin fraction has been offered as additional immunologic evidence of the frequent occurrence of antecedent streptococcal infection. Some investigators are of the opinion that an abnormal immune response to streptococcal infection in the host is an important factor in the pathogenesis of rheumatic fever.[8] Evidence in support of this concept is lacking. It was considered possible that if host susceptibility in the immunologic sense is a genetic character, electrophoretic studies of the blood proteins of rheumatic subjects who experienced various infections would be informative.[9]

MATERIAL AND METHODS

Material: During the period 1945 to 1947, 79 blood specimens from 42 rheumatic children were taken for electrophoretic analysis.

These children were either ambulatory patients attending the Cardiac Clinic, or children admitted to the pavilions of the New York Hospital with acute rheumatic fever. The records on antecedent illness for the majority of the patients were obtained from our own observation. In a few of the hospital patients the information was historical. The diagnosis of rheumatic fever was based on the presence of at least one major manifestation of the disease.[10]

Methods: The experimental procedures followed have been described in a previous communication.[11]

RESULTS

The observations presented in the preceding study of electrophoretic patterns in non-rheumatic children demonstrated that the gamma globulin component was increased in apparently healthy children when they had experienced an antecedent illness.[11] The data for the rheumatic subjects were therefore analyzed in relation to illness prior to the time that the blood specimen was obtained.

From the New York Hospital and the Department of Pediatrics, Cornell University Medical College.

This study was aided by a grant from the Commonwealth Fund.
(Received for publication June 8, 1948.)

During the period of observation, about one-half of the group experienced a respiratory illness. Of these, about half developed rheumatic fever in a period of time varying from less than one week to several months subsequent to the respiratory illness. About one-third of the group of rheumatic children who did not have a respiratory illness developed rheumatic fever.

TABLE I

ELECTROPHORETIC AND IMMUNOLOGICAL DATA FOR 42 RHEUMATIC PATIENTS

Case No.	Spec. No.	Date	Man. of RF	Antecedent illness		Complement titer	A.S. titer	Strep. Agg.		Electrophoretic pattern					
				type	interval			S_1	S_2	A	α_1	α_2	β	ϕ	γ
1	296	6-10-46	None	None	—	0.0050	—	0	0	64.5	1.1	16.4	11.5	—	6.6
2	65	9- 8-45	None	None	—	0.0026	—	20	40	51.1	4.4	6.9	16.4	7.2	13.9
3	172	1-26-46	None	None	—	—	—	10	0	57.1	4.1	9.4	9.7	7.3	12.3
4	173	1-26-46	None	None	—	—	—	—	40	56.5	5.2	8.3	11.0	6.5	12.5
5	521	3- 3-47	None	None	—	0.0053	—	—	40	61.5	4.7	11.0	10.2	—	12.6
6	99	9-22-45	None	None	—	—	—	20	0	60.0	4.5	9.3	11.5	5.5	9.1
	136	12-22-45	None	None	—	0.0065	—	0	0	54.7	7.7	10.3	12.2	6.3	8.5
7	483	2-14-47	None	None	—	0.0051	—	20	20	53.2	7.5	11.9	14.7	—	12.5
8	243	5- 8-46	Chorea	N.R.	—	0.0050	—	160	160	49.6	7.2	11.9	12.0	—	19.1
	339	8-12-46	"	"	—	0.0056	—	—	20	53.5	6.4	8.2	13.1	—	18.7
9	346	8-28-46	Chorea	None	—	0.0079	—	20	20	51.3	5.9	8.9	14.0	—	19.6
10	269	5-20-46	Chorea	None	—	0.0052	—	0	20	65.2	3.2	10.3	11.1	—	10.1
11	599	5-16-47	Chorea	None	—	—	—	—	—	59.6	7.0	11.1	14.1	—	8.0
12	194	3- 9-46	Poly.	None	—	0.0048	—	40	10	33.3	10.2	17.7	11.1	14.5	13.0
	261	5-12-46	None	U.R.I.	16 days	0.0045	—	20	0	41.1	7.0	13.9	12.0	—	24.3
13	568	4-19-47	Poly. Nod.	None	—	0.0044	—	10	—	60.5	5.6	9.8	11.0	—	12.9
14	108	9-29-45	Arth. Ery. Mult.	None	—	—	—	0	0	48.4	6.5	10.2	13.6	9.4	11.9
	259	5- 8-46	None	None	—	—	—	—	10	57.5	7.8	12.0	14.3	—	8.4
15	391	12- 7-46	Arth. Peri.	None	—	—	—	—	40	25.2	13.7	24.6	21.9	—	14.6
	412	12-20-46	"	"	—	—	—	320	160	34.4	11.6	22.3	19.5	—	12.2
	429	1- 6-47	"	"	—	0.0044	—	—	40	43.8	7.0	16.0	16.3	—	16.7
	442	1-17-47	None	None	—	—	—	320	80	52.8	7.9	10.9	14.6	—	13.6
	613	5-24-47	None	S.T.	3 wk.	—	—	0	0	51.9	7.1	12.1	15.4	—	13.4
16	159	1-12-46	None	S.T.	3 mo.	0.0053	—	—	20	51.0	9.1	7.7	8.0	5.5	18.7
17	143	12-29-45	None	S.T.	26 days	0.0059	—	—	0	53.8	15.2	10.3	9.3	9.4	11.8
	193	3- 9-46	"	"	3 mo.	0.0037	—	20	40	54.0	5.2	10.1	13.1	6.8	10.8
	533	3-18-47	"	S.T.	2 mo.	0.0037	—	0	80	44.1	6.9	13.1	13.4	—	22.4
	580	4-21-47	"	"	3 mo.	0.0045	—	40	40	46.4	7.6	10.1	15.0	—	20.8
	630	6- 8-47	Chorea	None	5 mo.	0.0040	—	10	80	51.2	8.1	13.1	9.5	—	17.8
18	85	9-15-45	None	S.T.	8 mo.	0.0050	—	80	—	42.0	6.8	14.2	10.8	8.9	17.3
19	73	9-10-45	None	None	—	0.0053	—	—	—	68.1	4.3	5.8	13.4	3.5	4.8
	202	3-23-46	Chorea	S.T.	1 mo.	0.0047	400	40	40	53.9	9.1	6.0	10.9	—	19.9
	484	2-14-47	None	U.R.I.	—	—	—	—	10	48.3	7.2	13.9	10.2	—	20.4
20	541	3-22-47	None	S.T.	23 days	0.0063	—	20	20	47.5	5.6	9.8	13.6	—	23.9
21	569	4-11-47	None	U.R.I.	5 mo.	0.0042	—	10	—	49.2	6.6	9.2	12.5	—	22.3
22	426	1- 4-47	None	U.R.I.	3 mo.	0.0047	—	—	40	54.8	5.2	9.2	14.7	—	15.9
23	213	4- 6-46	None	None	—	0.0064	—	80	40	52.2	7.0	10.0	16.7	—	14.1
	421	12-27-46	"	S.T.	1 wk.	—	—	20	20	45.5	8.1	9.3	21.1	—	15.8
	435	1-11-47	"	"	3 wk.	0.0043	—	10	20	32.7	6.2	14.0	13.9	—	33.1
	490	2-15-47	"	"	2 mo.	0.0045	—	20	80	45.7	8.0	9.7	17.4	—	19.1
	579	4-26-47	None	U.R.I.	2 mo.	0.0044	—	—	—	56.5	5.6	7.8	9.3	—	20.8
24	81	9-15-45	None	S.T.	3 wk.	0.0048	—	160	—	43.2	5.0	13.0	12.9	6.3	19.2
25	63	8-29-45	None	U.R.I.	1 mo.	0.0030	—	160	—	63.9	3.0	8.3	11.8	6.2	6.2
26	109	9-29-45	None	S.T.	1 wk.	—	—	40	40	49.2	4.6	8.4	11.1	3.9	22.6
27	183	2- 9-46	None	S.T.	1 day	0.0040	—	10	80	54.7	5.3	10.2	11.9	5.7	11.8
28	618	5-28-47	Poly.	Tons.	40 days	—	—	—	80	37.5	9.4	21.9	9.5	—	21.6
29	231	4-27-46	Chorea	Sinusitis	1 mo.	0.0043	300	80	40	34.3	3.2	15.2	12.9	—	34.4
	482	2-14-47	None	None	—	0.0051	—	—	40	59.1	10.5	11.3	10.1	—	8.9
30	275	5-25-46	Arth. Ery. Mult.	S.T.	3 mo.	0.0225	—	160	40	44.4	7.3	12.9	14.0	—	21.3
31	590	5- 9-47	Ery. Mult.	S.T., C.A.	2 wk.	0.0062	—	160	—	50.8	9.5	11.6	10.7	—	17.4

TABLE I—(*continued*)

Case No.	Spec. No.	Date	Man. of RF	Antecedent illness: type	Antecedent illness: interval	Complement titer	A.S. titer	Strep. Agg.: S_1	Strep. Agg.: S_2	Electrophoretic pattern: A	α_1	α_2	β	ϕ	γ
	621	5-29-47	"	"	1 mo.	0.0057	—	—	160	48.5	6.3	12.4	13.5	—	19.1
32	462	1-29-47	Poly.	U.R.I.	1 mo.	0.0062	—	80	40	54.4	9.6	7.3	10.3	—	18.3
33	676	7-15-47	Poly.	—	3 wk.	—	—	—	20	37.4	12.8	21.3	8.0	—	20.5
34	171	1-26-46	None	U.R.I.	During	—	—	40	40	58.8	3.6	9.4	11.0	8.1	9.0
	205	3-23-46	Poly., Card.	S.T.	3 wk.	—	—	—	160	39.7	5.2	10.3	17.1	—	27.7
	223	4-20-46	"	"	6 wk.	0.0057	—	320	40	34.4	7.8	13.8	10.9	—	33.0
	369	11-12-46	None	S..T.	5 mo.	0.0052	—	40	10	51.9	7.1	10.9	13.2	—	16.9
35	342	8-14-46	None	S.T.	4 wk.	—	—	40	160	—	—	—	—	—	—
	359	10-17-46	Poly. Card. C.F.	U.R.I.	2½ mo.	0.0073	—	—	40	57.0	11.9	16.1	10.9	—	4.1
	413	12-20-46	"	"	5 mo.	—	—	—	—	45.8	5.6	8.8	12.7	—	27.0
	447	1-22-47	"	S.T.	21 days	0.0300	—	—	—	43.2	7.5	9.4	17.7	—	22.0
36	615	5-26-47	Poly. Card.	S.T.	3 mo.	0.0030	—	80	160	49.7	9.8	12.0	12.4	—	21.0
37	270	5-20-46	Poly.	U.R.I.	2 wk.	0.0062	500	0	0	54.0	7.2	10.4	11.7	—	16.8
	486	2-14-47	None	N.R.	—	0.0066	—	—	20	60.2	7.4	12.7	9.4	—	10.2
38	67	9 -8-45	Poly.	Sc.F.	1 mo.	0.0030	—	160	—	47.0	6.0	9.9	11.3	6.8	18.8
39	241	5- 2-46	Card.	S.T.	3 mo.	0.0046	—	0	20	36.2	8.7	16.4	9.9	—	28.7
	266	5-24-46	Nod.	N.R.	—	0.0064	1000	—	10	39.3	8.3	15.5	13.4	—	23.4
	485	2-14-47	—	U.R.I.	8 mo.	0.0055	—	—	160	39.9	5.1	8.6	16.0	—	10.3
40	622	5-31-47	Poly.	S.T.	18 days	0.0025	—	0	40	36.2	9.6	18.8	11.5	—	23.8
41	138	12-26-45	None	U.R.U.	During	—	—	—	80	49.5	8.4	10.7	9.2	6.3	15.7
	297	6-10-46	Card.	S.T.	1 wk.	0.0068	—	20	20	49.5	6.4	7.0	15.3	—	21.7
	330	8- 1-46	Inactive	—	—	0.0052	400	20	20	54.1	5.6	7.6	15.5	—	24.0
	522	3- 4-47	Ac. Card. Failure	U.R.I.	1 mo.	—	—	—	160	32.9	8.5	15.9	12.8	—	29.8
42*	347	8-28-46	None	Asthma	1 mo.	—	—	—	—	54.3	4.8	8.0	11.0	—	21.9
	432	1- 6-47	Jt.P. Fever	—	—	0.0053	—	10	20	38.9	8.8	14.5	14.9	—	22.9
	448	1-22-47	"	—	—	0.0050	—	0	0	36.3	9.2	11.2	16.3	—	26.9
	458	1-27-47	"	S.T.	2 days	0.0040	—	0	—	39.9	8.5	13.2	13.1	—	25.2
	488	2-15-47	Nod.	—	—	—	—	—	—	38.2	5.7	10.2	13.4	—	32.4
	507	2-24-47	Afebrile	Allergic Rhinitis	—	0.0044	—	20	—	42.1	5.7	12.3	12.1	—	27.8
	573	4-23-47	"	"	3 wk.	0.0038	—	160	—	45.8	4.6	8.1	13.9	—	27.5

Key: Poly. —Polyarthritis
Card. —Carditis
C.F. —Congestive Failure
S.T. —Sore Throat
C.A. —Cervical Adenitis
Jt.P. —Joint Pains
U.R.I.—Upper Respiratory Infection
Tons. —Tonsillitis
Nod. —Nodules
Arth. —Arthritis
Arth. Peri —Arthritis Pericarditis
Ery. Mult. —Erythema Multiforme
Complement—Average (.0040–.0009)
S_1—Beta Hemolytic Streptococcus; A B 13 ("Positive" 160)
S_2—Beta Hemolytic Streptococcus; Group A 14
Normal Electrophoretic Pattern:

Mean—	A	α_1	α_2	β	ϕ	γ
	59.3	4.9	9.5	12.6	5.3	9.5
S.D. —	6.9	1.5	2.0	2.9	1.8	3.6

A.S. —Antistreptolysin Titer; Data obtained from Irvington House and St. Francis Sanatorium for Cardiac Children.

* The differential diagnosis between rheumatic fever and rheumatoid arthritis is not established.

In Table I, 79 electrophoretic studies of blood protein in 42 rheumatic children are presented in relation to antecedent illness and rheumatic status. In addition, complement titers, streptococcal agglutinins and antistreptolysin titers are presented for the same blood specimens.[12, 13]

Analysis of the data revealed that the electrophoretic patterns for the rheumatic subjects who did not experience either an antecedent respiratory illness or rheumatic fever were within normal limits. (Cases 1 to 7)

Electrophoretic patterns of children who developed rheumatic fever, (Cases 8 to 15) but had not experienced an antecedent respiratory infection did not demonstrate an increase in the gamma component. During febrile periods one or both alpha globulin components were usually elevated. The complement activity and streptococcal agglutinins were within normal limits in the majority of these patients. Children experiencing a respiratory illness prior to the time the blood specimen was obtained but who did not develop rheumatic fever (Cases 16 to 27) showed significant elevation of the gamma globulin component. Normal complement titers were observed in the majority of specimens studied.

The electrophoretic patterns of children who developed rheumatic fever *subsequent* to respiratory illness (Cases 28 to 41) also showed significant increases in the gamma globulin component. The antistreptolysin titers and streptococcal agglutinins were elevated. Complement activity was normal in the majority of tests.

Serial electrophoretic studies revealed that frequently the gamma component was elevated within three weeks following respiratory illness and in some instances remained at abnormally high levels for several months, regardless of whether the subjects developed rheumatic fever or not. Children experiencing repeated respiratory illness maintained high gamma globulin levels for prolonged periods. The albumen component was usually lowered in specimens with elevated globulin levels. The beta globulin and fibrinogen levels were normal in all but two of the determinations. In all of the patients, the total serum or plasma protein levels were within normal limits.

In Figure 1, serial electrophoretic patterns are presented for three representative patients. In Figure 1A (Case 23) there is a gradual elevation in the gamma globulin component. This patient experienced a respiratory illness without subsequent rheumatic fever. The electrophoretic pattern in Figure 1B (Case 34) for a patient who developed rheumatic fever subsequent to a respiratory illness demonstrates elevation of the gamma and the alpha globulin components. In Figure 1C (Case 15) there is no elevation of the gamma globulin component for a patient who developed rheumatic fever without an antecedent respiratory illness. The alpha globulins were markedly increased early in the course of the disease.

Comment

In published studies of the electrophoretic patterns in various abnormal conditions, the effect of antecedent illness has not usually been considered. It is well known that following streptococcal infection increased antibodies may be present for prolonged periods. High antistreptolysin titers have been observed for as long as one year following infection. Dole, Watson, et al[5] observed elevated gamma globulin levels in patients with scarlet fever, three of whom developed rheumatic fever.

Chow,[15] from a series of 198 determinations on patients with several diseases concluded that lowered albumen levels and elevated alpha globulins were a reflection of

some fundamental mechanism, and not necessarily characteristic of a specific disease. The increase in one or both alpha components is commonly observed in febrile states and following severe trauma such as fractures.[16]

Our observations demonstrate that elevation of the gamma globulin component is

FIGURE 1

SERIAL ELECTROPHORETIC PATTERNS ON 3 TYPICAL RHEUMATIC SUBJECTS

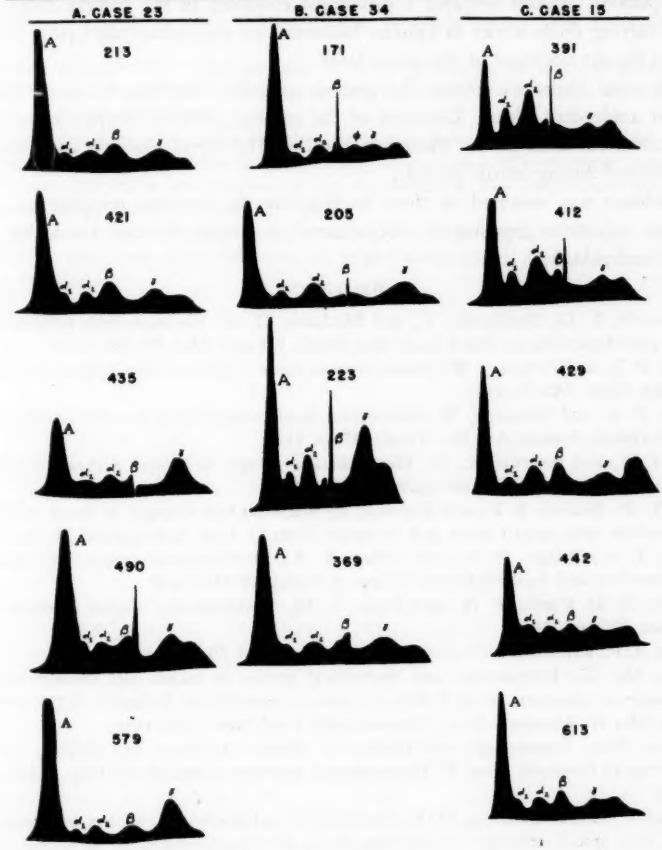

FIG. 1. Serial electrophoretic patterns on three typical rheumatic subjects: A. Inactive rheumatic patient with antecedent respiratory illness; B. Active rheumatic fever following antecedent respiratory illness. C. Active rheumatic fever with no antecedent respiratory illness.

not a function of the rheumatic process but a reflection of previous infection. The increase in the alpha globulins observed during febrile periods probably is a reflection of the exudative phase of the rheumatic process. The ingestion of salicylates, as Dyer et al[17] have shown, did not appear to affect the fibrinogen level.

It is apparent that the immunologic response of the rheumatic subject to infection which is presumably streptococcal in origin is no different from that of the non-rheumatic

subject. It was also observed that rheumatic fever was not a necessary sequel to such infection.

Summary

Electrophoretic analyses are presented for 79 specimens of blood plasma or serum from 42 rheumatic subjects during apparent health, following respiratory illness, and during rheumatic fever.

Electrophoretic studies revealed a prolonged elevation in the gamma component for a period varying from weeks to months following an antecedent respiratory illness with or without the development of rheumatic fever.

During acute rheumatic fever, the gamma globulin component was normal in the absence of antecedent illness. Elevation of the gamma globulin component in rheumatic fever is not a function of the rheumatic process. The alpha globulin components were usually elevated during febrile periods.

No evidence was obtained in these studies that the immune response of rheumatic subjects to infections presumably streptococcal in origin differed from that of non-rheumatic individuals.

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SPANISH ABSTRACT

Estudios Inmunologicos y Bioquimicos en Infantes y Niños con Referencia Especial a la Fiebre Reumatica

VI. Modelos Electroforeticos del Plasma Sanguineo y el Suero en Niños Reumaticos

Se presenta una correlación del cambio en el modelo electroforético del plasma y del suero con la fiebre reumática.

Se presentaron análisis electroforéticos de 79 muestras de plasma sanguíneo o de suero de 42 niños reumáticos en aparente salud, después de una enfermedad respiratoria, y durante la fiebre reumática.

Los estudios electroforéticos revelaron una elevación prolongada en el componente gama por un período variando de semanas a meses después de una enfermedad respiratoria anterior con o sin el desarrollo de la fiebre reumática.

La elevación del componente gama-globulina durante la fiebre reumática aguda fué normal en casos donde no había habido enfermedad antecedente. La elevación del componente gama-globulina en la fiebre reumática no es una función del proceso reumático. Los componentes alfa-globulinos subieron generalmente durante los períodos febriles.

No se obtuvo ninguna prueba de estos estudios de que la respuesta inmune de los niños reumáticos a las infecciones presumiblemente de origen estreptocócico difieren de la de los niños que no son reumáticos.

525 E. 68th St.

Pediatrics

VOLUME 2 NOVEMBER 1948 NUMBER 5

AMERICAN ACADEMY OF PEDIATRICS, INC. PROCEEDINGS AND REPORTS

Round Table Discussion

ACIDOSIS AND ALKALOSIS

ALEXIS F. HARTMANN, M.D., *Chairman, St. Louis, Mo.*

Acidosis and alkalosis are terms used to describe opposite types of disturbance of acid-base balance of the body fluids. From the chemical point of view acidosis may be defined as the condition in the blood characterized by a reduction of the $\frac{BHCO_3}{HHCO_3}$ ratio, and alkalosis as an increase. When $BHCO_3$ is primarily affected, the disturbance is referred to as metabolic in origin; when $HHCO_3$ concentration is the first to be altered, the resulting change is considered to be of respiratory origin. Primary changes of either $BHCO_3$ or $HHCO_3$ usually stimulate compensatory changes in the other which tend to restore the original normal ratio. When compensation for acidosis is incomplete, an increased H^+ ion concentration (decreased pH) of the blood results, and such a change is referred to as acidemia. The opposite condition is called alkalemia.

From the clinical point of view a much broader concept of acidosis and alkalosis exists and includes in addition all related changes in metabolism (carbohydrate, fat, protein, water, mineral, enzyme) which may give rise to definite symptoms and signs of illness. Such metabolic changes may be either primary or secondary, and, as either, may be very important in determining prognosis as to life or death.

In practice one is prompted to consider the possibility of acidosis or alkalosis by noting suspicious signs or symptoms and then diagnoses with certainty the presence and extent of change by chemical determinations of serum CO_2 content and pH.

The most important signs and symptoms of acidosis are: hyperpnea, which is considered not primary, stupor, dehydration, ketosis and strongly acid urine. Any or all may be absent. The most important signs and symptoms of alkalosis are: depressed respiration, considered compensatory, or hyperventilation, considered primary, tetany, and forceful vomiting, thought to be the result of pyloric or high intestinal obstruction, and strongly alkaline urine. Again any or all such symptoms may be absent. Furthermore, ketosis may be associated with alkalosis; secretion of alkaline urine may give rise to acidosis, and alkalosis may be accompanied by formation of acid urine. Also, it is not unusual to see in the same subject conditions favoring the development of both acidosis and alkalosis, but with the presence of neither.

For absolute diagnosis of acidosis or alkalosis two of the three variables, $BHCO_3$, $HHCO_3$ and pH have to be determined. Since pH and $BHCO_3$ usually move in the same direction, it has been widespread clinical practice to determine only $BHCO_3$ by determining serum CO_2 content by the Van Slyke manometric method. In this connection it should be remembered that when so determined

From the Annual Meeting of the American Academy of Pediatrics, Dallas, Tex., December 8-11, 1947.

about 20/21 of the CO_2 comes from $BHCO_3$, the remainder coming from $HHCO_3$. In the past it was customary not to separate $BHCO_3$ and $HHCO_3$, but to record them together as the total CO_2 content. If separated, $BHCO_3$ was recorded either as volumes percent, as millimols per liter or as milliequivalents B^+ per liter. $HHCO_3$ was recorded particularly as CO_2 tension mm.Hg. But also it was sometimes recorded as volumes percent CO_2, millimols per liter, or milliequivalents H^+ per liter. The tendency at present is to record $BHCO_3$ and $HHCO_3$ in mM. per liter.

Since, as mentioned before, $BHCO_3$ and pH usually move in the same direction, and since it is common clinical practice to rely on determination only of serum CO_2 content to diagnose the existence and severity of acidosis and alkalosis, the following criteria will be used in later discussion. (Tables I and II.)

TABLE I

CLASSIFICATION OF SEVERITY OF ACIDOSIS

Values expressed as mM/l.*

Extreme Acidosis	*Moderate Acidosis*
CO_2 cont. less than 7	CO_2 cont. 11.4–16.8
$BHCO_3$ less than 6.4	$BHCO_3$ 10.7–14.8
Severe Acidosis	*Mild Acidosis*
CO_2 cont. 7–11.4	CO_2 cont. 16.8–20.4
$BHCO_3$ 6.4–10.6	$BHCO_3$ 14.9–19.1

* mM/l. × 2.2 = vols. per 100 cc.

TABLE II

CLASSIFICATION OF SEVERITY OF ALKALOSIS

Values expressed as mM./l.

Extreme Alkalosis	*Moderate Alkalosis*
CO_2 cont. more than 45	CO_2 cont. 36–41
$BHCO_3$ more than 42	$BHCO_3$ 34–38
Severe Alkalosis	*Mild Alkalosis*
CO_2 cont. 41–45	CO_2 cont. 32–36
$BHCO_3$ 38–42	$BHCO_3$ 30–34

ETIOLOGY AND INCIDENCE OF ACIDOSIS AND ALKALOSIS

Metabolic Acidosis: During the 24 year period 1923-46, inclusive, 1465 cases of acidosis characterized by reduced serum CO_2 content were diagnosed in patients in the St. Louis Children's Hospital. The total incidence was approximately 2% of all hospital admissions. Severe disturbance of digestion, particularly severe diarrhea, accounted for about 43% of the total number, while diabetes mellitus, renal disease, and severe infections each accounted for an additional 14%, and all other causes together accounted for the remaining 43%. The relative incidence of each group during the second half of the study period was similar to that noted in the first half, although almost twice as many cases were diagnosed in the latter half of the study.

A detailed analysis of etiology and incidence will be found in Table III.

Acidosis Associated with Diarrhea and Vomiting—Pathogenesis: This type of acidosis seems to result usually from the combined effects of a number of factors:

1. Loss of gastro-intestinal secretions: Experimentally in healthy dogs loss only of gastric juice by fistula or vomiting leads primarily to a chloride deficit—bicarbonate excess type of alkalosis—while loss only of pancreatic juice leads primarily to a bicarbonate deficit acidosis, and in each instance the result is what should have been expected from the composition of the two secretions,

gastric juice being highly acid with much more "fixed" acid (chloride) than fixed base, and pancreatic juice being highly alkaline with much more fixed base than fixed acid. If an obstruction or fistula is created high in the small intestine (terminal duodenum) so that gastric juice, pancreatic juice, bile and some succus entericus are lost, chloride deficit always results, sometimes partly compensated for by retention of bicarbonate (alkalosis), sometimes in association with diminution also of bicarbonate (acidosis), and sometimes with no change in bicarbonate. With lower (ileocecal) intestinal obstructions or fistulae similar variable but much less extensive chemical changes result, undoubtedly because of smaller losses of gastro-intestinal secretions due to considerable reabsorption in the small intestine. There seems to be a slight but definitely greater tendency for development of alkalosis than acidosis, suggesting that loss of gastric juice predominates over loss of pancreatic juice. A plausible conjecture for this fact would be that because of the relatively small size of the pancreatic duct, and lack of distensibility of the pancreatic acini, increased intra-intestinal pressure

TABLE III

CLINICAL CLASSIFICATION AND INCIDENCE OF METABOLIC ACIDOSIS

I. Diarrhea and Vomiting		645	IV. Severe Infection or Moribund State		186
A. Specific enteritis	116		A. Pneumonia, etc.	82	
B. Nonspecific diarrhea	517		B. Sepsis and Moribund State	104	
C. Intestinal Obstruction or Fistula	22				
			V. Miscellaneous		207
II. Diabetes Mellitus		209	A. Non-diabetic Ketosis	42	
			B. Convulsions	35	
III. Renal Disease		208	C. Congenital Heart Disease	8	
A. Nephritis	140		D. Acquired Heart Disease	8	
B. Anatomic Anomalies	57		E. Acid Administration	6	
C. Functional Insufficiency Exclusive of A and B	11		F. Salicylate Intoxication	24	
			G. Athrepsia	30	
			H. Hypoglycemia	4	
			I. Other Causes	50	

affects the pancreas more than the stomach, which is distensible and can, through vomiting reduce its pressure. In infants and children gastro-intestinal obstruction and fistulae produce similar chemical changes. Because disease, however, may be the cause of loss of gastro-intestinal secretions and because the original quality or quantity of secretions may be altered by the disease process, more variable results are noted in clinical practice than in the experimental laboratory. Thus considerable loss of gastric juice can result from vomiting associated with infections such as otitis media in infants without development of alkalosis because the infectious process leads to marked reduction in the hydrochloric acid content of the gastric juice. On the other hand the chronic diarrhea of pancreatic fibrosis is apt to lead to alkalosis instead of acidosis, because with fibrosis of the pancreas there is much diminution of secretion of alkaline pancreatic juice, whereas gastric secretion may be altered but little.

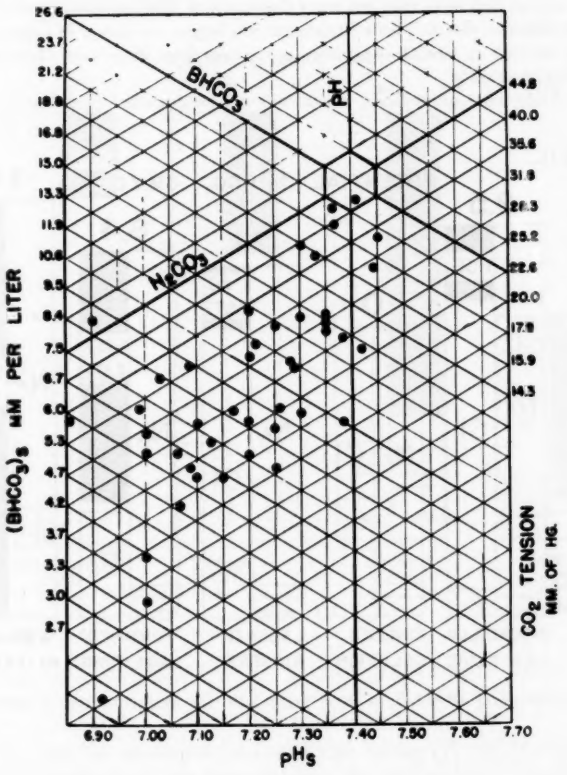
2. Dehydration: When sufficient anhydremia (hemoconcentration) accompanies dehydration the reduction of plasma volume may result in so much reduction of blood flow that anoxemia and tissue anoxia develop and lead to accumulation of lactic acid in the blood and body fluids. The lactate ion displaces the bicarbonate ion from combination with fixed base and sometimes accounts for half or more of the bicarbonate reduction observed.

3. Renal Insufficiency: Oliguria alone, if sufficiently marked, may deprive the subject of full benefit of renal defense against acidosis in that just not enough highly acid urine with the NH_4 ion substituted for Na and K is secreted, with resultant retention of "fixed" acids, particularly Cl. The normally low "clearance" capacity of the young infant's kidney, especially for Cl., adds to the effects of oliguria, and any actual renal pathology or development anomaly may reduce renal function still more. Impairment of renal defense against either acidosis or alkalosis may result.

4. Adrenal insufficiency: It seems quite possible that sometimes in very young infants adrenal cortical deficiency may interfere with renal defense against acidosis by stimulating secretion of alkaline urine of high water content.

5. Respiratory failure: Compensatory hyperventilation, resisting development of acidemia, fails quickly in young and debilitated infants and may never occur in feeble premature babies.

6. Miscellaneous: Occasionally ketosis exists (especially in acute bacillary dysentery) and the



INITIAL ACID-BASE BALANCES

IN ACUTE SEVERE DIARRHEA

CHART I

ketone acid accumulation behaves as does lactic acid. Sometimes medication is capable of producing acidifying effect, such as acetyl salicylic acid (aspirin) administration, where in addition to the acid effect per se, there exists also the possibility of salicylate intoxication with resulting severe ketosis. Chemotherapy may not be without effect. Sulfanilamide leads to primary secretion of alkaline urine which tends toward $BHCO_3$ deficit and produces methemoglobinemia favoring tissue anoxia. Para-aminobenzoic acid is acidifying per se. (To avoid possibility of acidosis, the sodium salt should always be used when large doses are administered.) p-Aminomethylbenzenesulfonamide (Sulfamylon) is converted into an acid in the body and is capable of producing acidosis.

In the case of one infant seen some years ago, diarrhea had been "treated" with (1) calomel which increased the loss of gastro-intestinal secretions; (2) aspirin which led to salicylate poisoning with the development of severe ketosis; (3) phenacetin which led to methemoglobinemia of great severity; and (4) paregoric which inhibited respiratory defense.

From a somewhat broader point of view, diarrheal acidosis also leads to deficiency of K as well as Na and to important losses of tissue proteins, liver and muscle glycogen, body fat, skeletal Ca and HPO_3, and vitamin stores, so that the complete clinical picture may often be complex and calling for a good deal more than just relief chemically of $BHCO_3$ deficit.

All acid-base balances obtained before treatment was begun are shown in Chart I. Then tendency for acidemia to increase as $BHCO_3$ diminishes is apparent from these data. Occasionally respiratory defense has failed completely.

Treatment: Aside from prophylaxis, which will not be discussed here, the treatment of severe

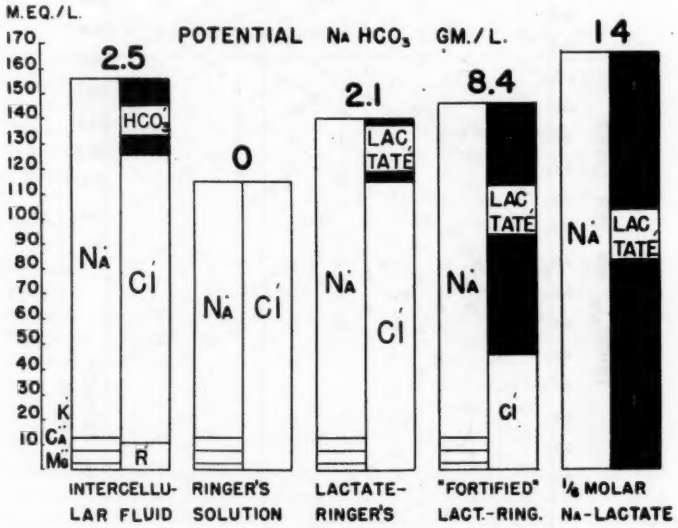


CHART II. Composition of solutions used principally for reconstitution of extracellular fluid.

diarrhea generally calls for: (1) prompt relief of acidosis, dehydration and anhydremia; (2) attempts to eradicate causative organisms from the gastro-intestinal tract or elsewhere by antibiotic therapy and chemotherapy; (3) placement of the gastro-intestinal tract at rest for as long a time as seems desirable; (4) parenteral feeding, which should be as complete as possible and (5) proper methods of resumption of enteral feeding.

Our present method of treatment at the St. Louis Children's Hospital may be outlined as follows:

1. Immediate administration, intravenously if possible, otherwise subcutaneously, of isotonic (1/6 molar) sodium lactate in an amount approximating 30 ml./kg. body weight. This step leads to prompt dilution of the blood, which is often extremely concentrated, and to increase in plasma volume and blood flow. Improvement of circulation frequently is manifested during the fluid administration by appearance of veins which previously had been invisible, change of skin color from ashen-gray to the usual pink, increase in blood pressure in the extremities, improvement in the quality of the pulse and enlargement of the heart, which during anhydremia, is often extraordinarily small. The latter change can best be appreciated by fluoroscopy. This first step also starts the relief of acidosis, independently of renal activity.

2. Complete relief of acidosis. In cases of acidosis known or judged to be very severe (CO_2 content of 1/mM./l. or less, equivalent to $BHCO_3$ concentrations of less than 10.5 mM./l.), 60 ml.

more of 1/6 molar sodium lactate per kg. body weight are added to two-thirds that volume (40 ml./kg.) of hypotonic Ringer's solution, and the mixture* is then given subcutaneously and/or intraperitoneally. Usually some six to 12 hours are required to complete this step. In the most extreme cases 30 ml./kg. more of the isotonic sodium lactate may be required. In cases of only moderate acidosis, such as may be expected to accompany the usual case of acute bacillary dysentery, a half dose of (30 ml./kg.) 1/6 molar sodium lactate added to 40 ml./kg. of Ringer's solution suffices.

This second step generally also relieves dehydration completely and restores more or less completely extracellular fluid electrolyte loss.†

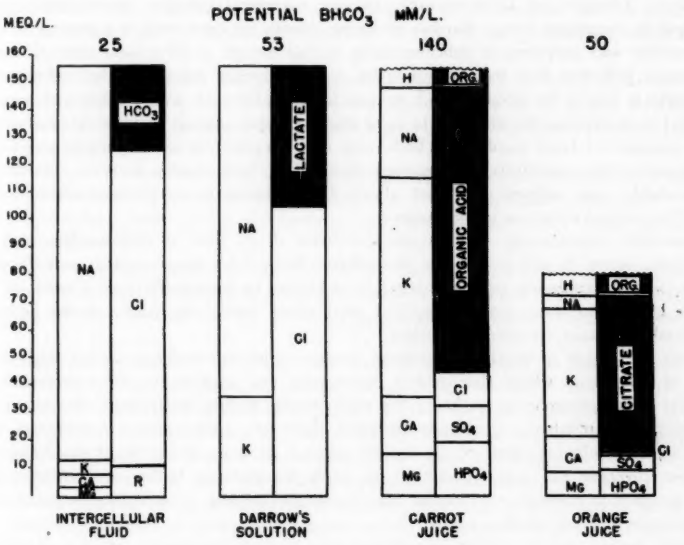


CHART III

* This mixture is usually referred to as "fortified" lactate-Ringer's solution. It, with other solutions mentioned in treatment as well as the composition of certain fruit and vegetable juices, is pictured in Charts II and III.

† Its effect in restoration of intracellular fluid is less certain. It is Darrow's belief that, because of previous potassium loss from the cells, a mixture richer in K and with less Na should be used, otherwise too much Na and not enough K will be retained by the cells. The composition of his solution (Chart III) is as follows: $NaHCO_3 = 4.4$ gm. or 52 mM./l.; $KCl = 2.7$ gm. or 36 mM./l.; $NaCl = 3.0$ gm. or 69 mM./l. Recent work would indicate that the total body content of Na is about 59 mEq./kg., more than 60% of which would be in extracellular fluid. Thirty ml./kg. of 1/6 molar Na-lactate is the equivalent of 5 mEq.Na/kg. Forty ml./kg. hypotonic Ringer's solution is the equivalent of slightly less than 4 mEq.Na/kg. In the largest amount of Na-lactate ever required (premature infant with extreme acidosis, acidemia and dehydration), Na would be administered to the extent of 24 mEq./kg. An infant taking 60 ml. of cow's milk per kg. body weight per day receives from milk alone 3 mEq.Na/kg. With normal mature renal function, urine often exceeds 160 mEq. Na/l. when there is indication for maximal excretion of Na. Therefore, it would seem that in our method of treatment of acidosis, there is little likelihood of over-administration of Na during the initial steps of parenteral administration.

The total body content of K on the other hand is about 76 mEq./kg. Forty ml./kg. of hypotonic Ringer's solution is the equivalent of .2 Mew. K/kg. Eighty ml. of Darrow's solution per kg. is the equivalent of 2.8 mEq.K/kg. One hundred and eighty ml./kg. of our D.A.S. No. 2 is the

The quantity of lactate administered is sufficient to abolish ketosis quite promptly if the latter exists (as it usually does in acute bacillary dysentery), and probably leads to some storage of liver glycogen. From recent work there is reason to believe that in these respects lactate is superior even to glucose. The total fluid volume administered is also usually sufficient to permit diuresis, which should be expected unless plasma protein deficiency exists and leads to edema and oliguria.

3. Transfusion of whole citrated blood provides a normal RBC and satisfactory plasma protein concentration (usually 20 ml./kg. repeated once or twice). Plasma in any of its commercially available states may be substituted for whole blood to insure proper plasma protein concentrations, but should be considered inferior to whole blood at this stage.

Antibiotic Therapy and Chemotherapy: Because parenteral infection seems frequently both to initiate and to complicate severe diarrhea in young infants, we have made it a practice to administer both penicillin and streptomycin subcutaneously in full dosage at three hour intervals until subsequent events indicated that their continuation was no longer necessary. Oral administration of streptomycin is also to be recommended, at least for a trial period, with the hope of possible beneficial effect in controlling the diarrhea. In some instances where gastric analyses revealed achlorhydria and the presence of large numbers of Esch. coli, oral streptomycin administration was followed by disappearance of the organisms and cessation of diarrhea. Such success, however, has by no means been invariable, and failures could not always be attributed to sterptomycin-resistant strains of Esch. coli, as seemed to be true in some cases.

Sulfonamide chemotherapy with poorly absorbable drugs such as sulfasuxidine and phthalylsulfathiazole, seems to add nothing to the effects obtained by drugs such as sulfadiazine, sulfamerazine, and sulfapyrazine since the latter, in addition to having effect as a result of diffusion from the blood into tissue everywhere, also exert action within the lumen of the bowel because a considerable fraction remains unabsorbed.

Because the danger of renal complications increases with the tendency toward oliguria and production of acid urine which characterizes dehydration and acidosis, we have preferred with the availability of streptomycin to withhold the sulfonamides unless bacteriologic studies of organism susceptibliity and resistance specifically indicated their use. Under such circumstances we prefer the subcutaneous administration of the sodium salts of all three of the drugs simultaneously, both to broaden coverage and lessen possibility of renal precipitation. Under such circumstances fluid therapy designed to prevent recurrence of dehydration and acidosis is carried to the point of securing large quantities of dilute alkaline urine.

Frequent gastric analysis and an opportunity once to study intestinal content at the level of the cecum have convinced us of the futility of trying to rid the stomach or small bowel of Esch. coli by oral administration of sulfaonamides. Apparently their effect is limited to the large bowel.

Rest of the gastro-intestinal tract by complete prohibition of oral feeding, formerly thought necessary in all severe cases, is now restricted to those infants who have a marked tendency to vomit. If vomiting is not an important symptom, or when it seems no longer to be readily induced by feeding, alimentation is begun and continued in the following manner:

1. What is termed D.A.S. No. 2 solution is made quite simply by mixing equal quantities of 10% dextrose, 10% amigen and a special salt mixture* designed to yield a final salt intake resembling that which would be taken if human milk were being fed, is at first diluted with two parts of water and fed ad libitum. Despite possible continuation of watery diarrhea, a positive fluid balance can be frequently maintained in this way. If not parenteral fluid therapy is continued in addition.

2. The D.A.S. solution is then given less diluted and then without dilution.

3. It is then alternated approximately every four hours with dilute formula feedings made of skimmed or half-skimmed evaporated or dried milk. We usually prefer lactic acid milks and the carbohydrate is usually dextrimaltose or Karo syrup, but sometimes may be glucose.

4. If the formula is then tolerated when fed at usual concentrations, the D.A.S. is discontinued between feedings.

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equivalent of 4.5 mEq.K/kg. Most fruit and vegetable juices are comparable to D.A.S. No. 2 in this respect. We prefer to administer K orally as an integral part of the first feedings in the form of our D.A.S. solution.

* $MgCl_2.6H_2O$ 0.875 gm./1., Ca-lactate 3.45 gm./1., K-lactate 0.545 gm./1.

During the early period of reduced oral feeding, parenteral feeding with amigen, dextrose, vitamin, whole blood and plasma, especially enriched plasma, are resorted to as outlined by Hartmann and Lawler.

In very critically ill infants me have come to prefer the use of concentrated serum albumin as a substitute for plasma. The latter has occasionally given rise to some tetany because of its citrate content and on a number of instances to hepatitis presumable because of contamination with virus. On the other hand the only reactions noted with contentrated serum albumin have been the result of either excessive dosage or too rapid administration.

If symptoms arise suggestive of calcium deficiency, Ca is administered at least for a clinical trial while special calcium studies are made. We have not, however, been impressed with its value except in very rarely encountered cases of hypocalcemia and in the cases receiving too much sodium citrate in plasma.

If acidosis is overtreated for any reason with resulting alkalosis, all potential alkali administration is temporarily discontinued; and if symptoms of alkalosis exist or if plasma $BHCO_3$ is in the range of extreme alkalosis, treatment with NH_4Cl is given, with CO_2-O_2 gas and $CaCl_2$ solution on hand for emergency use.

If infants receive such treatment for several days without very decided improvement, and especially if recurrence of dehydration seems unusually difficult to prevent, adrenal insufficiency is to be suspected and treatment with desoxycorticosterone and possibly also whole gland preparations cautiously attempted.

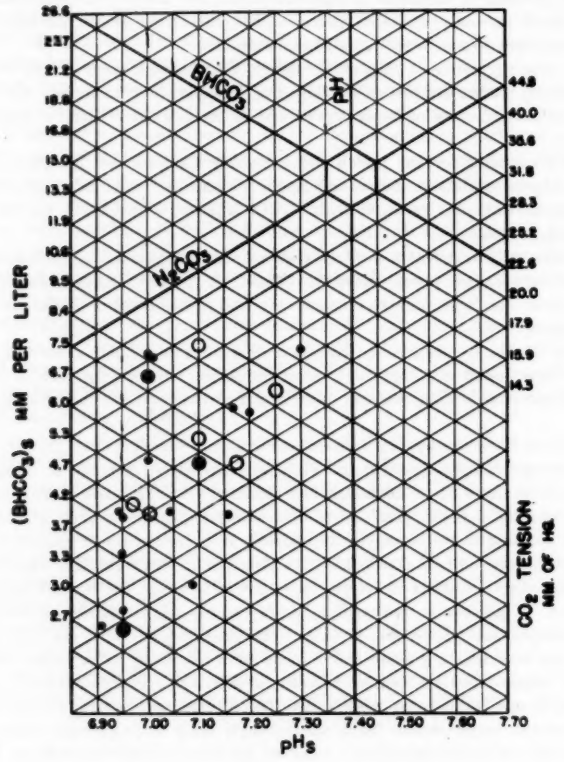
In most of our failures, uncontrolled infection or serious congenital anomalies or cerebral vein thrombosis have been found at autopsy to account for death. This was not true in earlier days when such complete parenteral feeding was not possible; then often no anatomic cause for death could be found.

Diabetic Acidosis-Pathogenesis: In infants and children the first link in the chain of events culminating in severe diabetic acidosis and coma appears to be reaction of insulin secretion. As result, there would be removal of inhibition (by pituitary [Houssay] and adrenal cortical hormones [Long]) of the reaction between glucose and adenosinetriphosphate to form glucose 6-phosphate—a reaction which is activated by the enzyme hexokinase. As a further result glucose would accumulate in the body at the expense of its conversion into glycogen and its oxidation with release of energy.

When sufficient hyperglycemia develops (approximately twice the normal fasting blood sugar level) the amount of glucose in glomerular filtrate exceeds the normal renal tubular capacity for complete reabsorption and glycosuria develops. The renal tubules also are limited in the extent to which they can concentrate glucose and require from 10 to 20 ml. of water for each gram of glucose excreted. Glycosuria thus leads to polyuria, at first well compensated for by polydypsia. Loss of potential food energy in the form of glycosuria (glucose being derived not only from carbohydrate food—100%, but also from protein 58%, and fat 10% leads to polyphagia (hunger) and loss of weight and strength. When the glycogen content of the liver becomes too reduced to allow for adequate energy from carbohydrate oxidation, fat oxidation increases with production of ketone bodies at a rate too rapid for metabolic removal by extra hepatic tissues—muscle chiefly. The acetone bodies then accumulate in the blood and tissue fluids and appear in abnormal quantities in the urine —a condition described as ketosis. The two ketone acids, B-hydroxybutyric and aceto-acetic, displace K from combination with weaker acids in the cells (carbonic acid, phosphates, hemoglobin and other proteins) and Na from similar bicarbonate, protein and phosphate buffers in the intercellular fluid compartments. The resultant reduction of $BHCO_3$ is by definition acidosis. The lowered $BHCO_3/HHCO_3$ ratio which results leads (1) to increased H ion concentration or acidemia causing other buffers to become weaker acids and release base in support of diminishing $BHCO_3$ and (2) to compensatory hyperventilation, usually described as hyperpnea or air-hunger (Kussmal breathing).

At about this time the liver enlarges rapidly due to fatty infiltration, becomes tender and leads to vomiting, which causes loss of Cl. and fixed base and accentuates dehydration already potentially produced by polyuria. Base economy practiced by the kidneys by secretion of urine of maximal acidity and substitution of the ammonium ion for fixed base is not 100% efficient and continued excretion of ketone acids in large amount leads to further loss of fixed base. Further loss of strength occurs and fluid intake decreases until anhydremia (hemoconcentration due to shrinkage of plasma volume) complicates dehydration. Anhydremia leads to more and more reduction of blood flow, first through the skin allowing leukocytes to concentrate in peripheral capillaries and

red oxyhemoglobin to become blue reduced hemoglobin with resultant ashen-grey pallor, and then in vital organs allowing accumulation of lactic acid because of anoxemia and tissue anoxia. Oliguria then replaces polyuria with renal functional failure. As a final event, cerebral functional failure may result and be manifested by coma, and general reduction of bodily resistance may lead to fatal terminal infection.



ACID–BALANCES BEFORE TREATMENT OF DIABETIC ACIDOSIS

○ NO ALKALI
● $NaHCO_3$
• Na-LACTATE

CHART IV

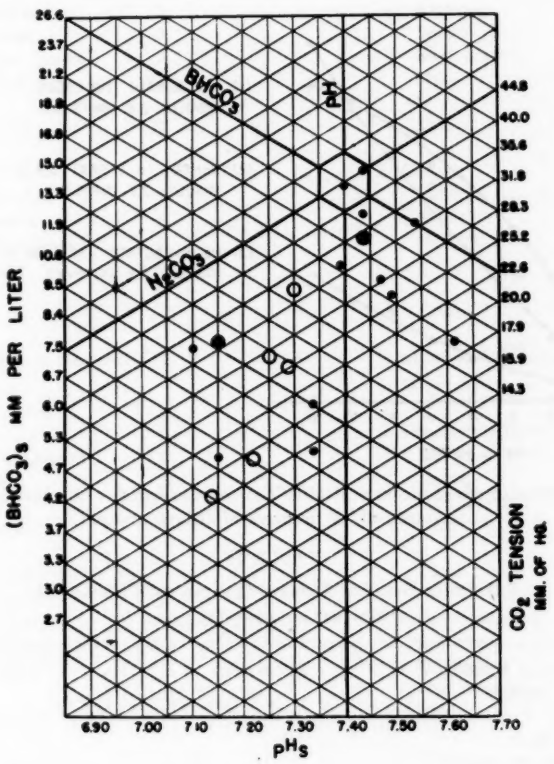
Treatment: In practice treatment is carried out in the following way:

Initial Treatment

1. Insulin—2 units/kg.
2. I.V. 1/6 M. Na-lactate—30 ml./kg. or 5 mM./kg.
3. Subcutaneous 1/6 M. Na-lactate—30 ml./kg. or 5 mM./kg.

At 6 hours

1. Insulin—1/2 ± unit/kg.
2. More subcutaneous 1/6 M. Na-lactate if necessary—5 mM./kg.
3. Plasma, concentrated albumin or whole blood if necessary.



ACID–BASE BALANCES

6 HOURS AFTER BEGINNING

TREATMENT OF DIABETIC

ACIDOSIS

○ NO ALKALI

● Na_2HCO_3

• Na-LACTATE

CHART V

Charts IV and V are plotted initial acid-base balances and their positions after six hours' treatment by one of the three methods.

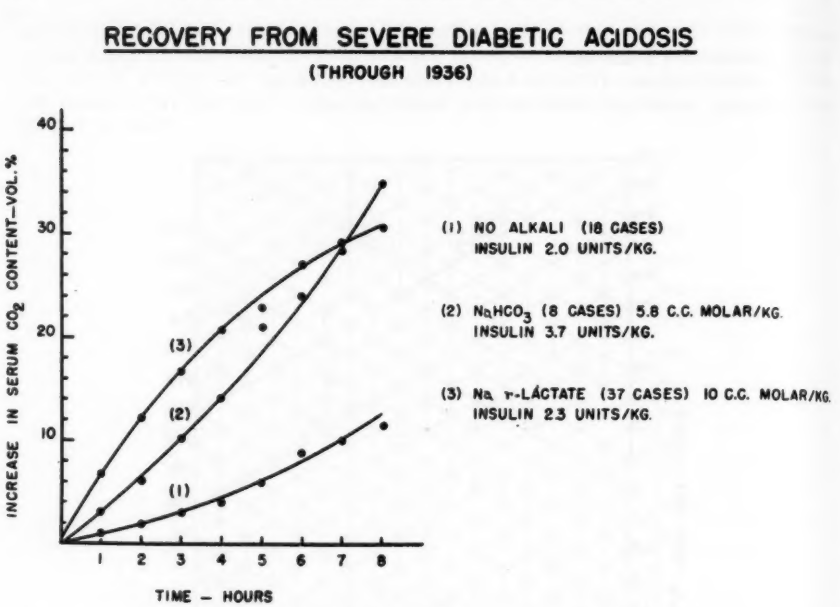


CHART VI. Mean speeds of recovery of ($BHCO_3$) to be expected in the three most commonly used methods of treatment of diabetic acidosis.

TABLE IV

RESULTS IN DIABETIC ACIDOSIS TREATED WITH NA-LACTATE
(1930–1947 inclusive, 133 Cases)

DEGREE ACIDOSIS (mM./l.)	RECOVERED	DIED
Extreme acidosis (CO_2 cont. less than 7) ($BHCO_3$ less than 6.4)	51	5 *Cause of death* Hyperpyrexia (1930) Pneumonia? (1931) Staph. sepsis (1935) Staph. sepsis (1938) Water intoxication (1938)
Severe acidosis (CO_2 cont. 7–11.3) ($BHCO_3$ 6.4–10.7 mM/l.)	48	0
Moderate acidosis (CO_2 cont. 11.3–15.9) ($BHCO_3$ 10.7–14.7)	24	0
Mild acidosis (CO_2 cont. 15.9–20.4) ($BHCO_3$ 14.9–19.1)	9	0

TABLE V

SEVERITY INCIDENCE OF ACIDOSIS OF RENAL TYPES

Glomerular Nephritis—40	
1. Acute or Subacute	
Extreme	0
Severe	3
Mod. Severe	3
Mild	14
Total	20
2. Chronic	
Extreme	1
Severe	6
Mod. Severe	7
Mild	6
Total	20
Suppurative Nephritis—14	
1. Acute	
Extreme	1
Severe	2
Mod. Severe	2
Mild	2
Total	7
2. Chronic	
Extreme	1
Severe	1
Mod. Severe	2
Mild	3
Total	7
Functional Insufficiency Without (?) Anatomical Anomalies	
Extreme	1
Severe	4
Mod. Severe	3
Mild	3
Total	11
Toxic Nephritis—8	
1. Acute	
Extreme	0
Severe	1
Mod. Severe	1
Mild	3
Total	5
2. Chronic	
Extreme	0
Severe	2
Mod. Severe	1
Mild	0
Total	3
Anatomical Anomalies—57	
1. Hypoplasia	3
2. Obstructive Hydronephrosis	
Extreme	1
Severe	1
Mod. Severe	7
Mild	13
Total	22
3. Other Anomalies	
Extreme	1
Severe	7
Mod. Severe	13
Mild	11
Total	32

Average response of serum CO_2 content (plasma $BHCO_3$) to the different treatments is shown in Chart VI.

Overall results in our entire series of Na-lactate treatment cases may be summarized as shown in Table IV.

Renal Acidosis-Pathogenesis: Acidosis may be associated with any type of nephritis or anatomic anomaly of the kidney capable of causing renal insufficiency, or with renal functional insufficiency without demonstrable anatomic changes in the kidney.

From Table V some idea can be obtained of the relative importance of the different renal

abnormalities in the production of acidosis and of its degree of severity, as noted in the latter half of this study.

In acute glomerular nephritis, if acidosis exists at all, it is likely to be mild and transient and due chiefly to lactic acid accumulation the result of convulsions, cardiac failure, or both. Data from one such case, with severe acidosis, however, is shown in Table VI. Occasionally severe renal insufficiency characterized by prolonged anuria accompanies acute glomerular nephritis, and retention of all acid end-products may be important in the production of severe acidosis. In one instance previously reported in some detail, despite the fact that retention of inorganic phosphorus reached

TABLE VI

CLETUS B., ACUTE GLOMERULAR NEPHRITIS WITH CONVULSIONS

mEq./l.	5-12-27	5-13-27
Chloride	108.0	101.0
HCO_3	*11.9 (−13)*	*17.1*
Proteinate	11.9	13.0
Inorg. HPO_4	2.4	3.4
Lactate	*12.2 (+11)*	*4.0*
p^Hs	7.13	7.39

TABLE VII

CATHERINE B., HEMO. STREP. SEPSIS AND ACUTE GLOMERULAR NEPHRITIS

mEq./l.	4-12-26	4-12-26	4-13-26	
Chloride	70.0 (−30)	64.0 (−36)	70.0 (−30)	(Alkalosis)
HCO_3	*21.0 (− 4)*	*29.0 (+ 4)*	*29.0 (+ 4)*	
Proteinate	16.0	16.0	15.0	
Inorg. HPO_4	9.0 (+ 6)	*10.0 (+ 7)*	*14.0 (+11)*	(Acidosis)
Total determined acid	116.0	119.0	128.0	
Total base	120.0 (−31)	120.0 (−31)	132.0 (−19)	(Acidosis)
p^Hs	7.35	7.40	7.45	

24.5 mg./100 ml. serum (binding base to the extent of 14.2 mEq./l. and that total base of the first two blood serum samples was but 120 mEq./l., no acidosis was noted because of the severe vomiting which had caused the loss of much hydrochloric acid, with resultant serum chloride concentration of only 64 mEq./l. A "balance sheet" of the plasma electrolytes in this interesting case is shown in Table VII.

In chronic glomerular nephritis the acidosis is likely to be both more severe and more persistent. It tends first to make its appearance in an insidious manner and seems the result of altered tubular function which leads to more chloride reabsorption than sodium. Urine is dilute and never strongly acid and the plasma electroylte pattern is characteristic of "chloride" acidosis with only slight reduction of total base and no retention of phosphate. Sudden illness involving vomiting, diarrhea, diminished fluid intake, diminished potential alkali intake, dehydration and oliguria can suddenly precipitate development of extreme degrees of acidosis in such children still without appreciable acid retention as may be noted from Chart VII. In the more terminal stages of the disease phosphate and sulfate retention make their appearance and contribute to the characteristic electroylte pattern of this stage.

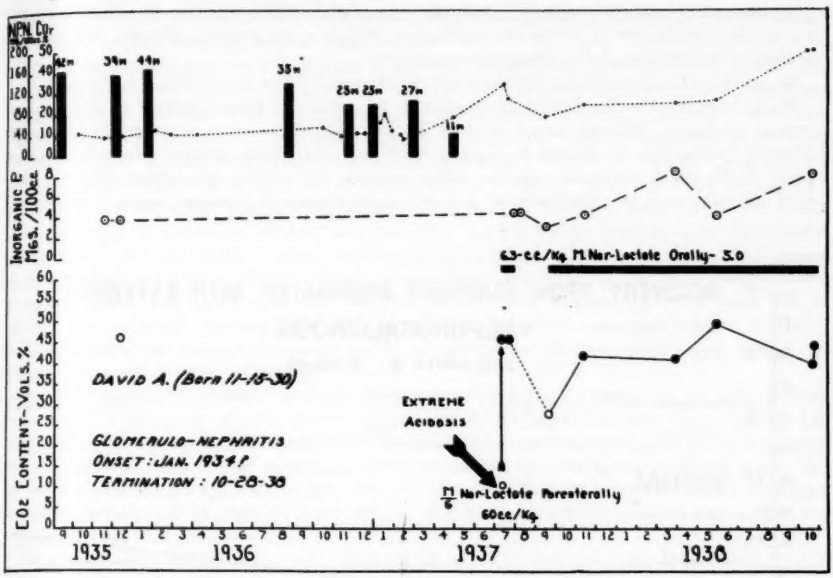
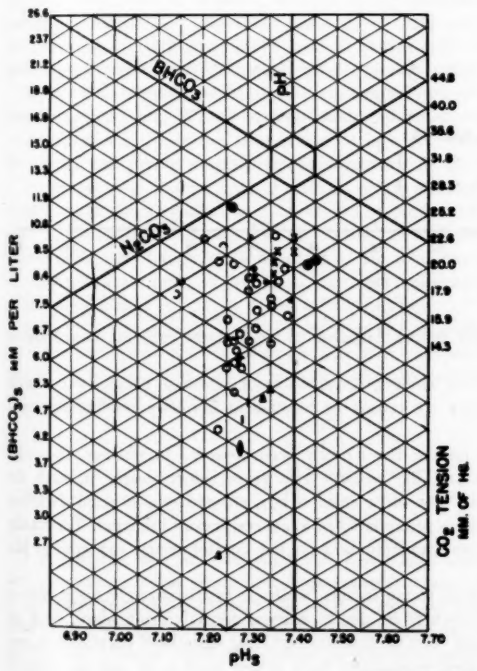


CHART VII



ACID-BASE BALANCES IN 10 UNTREATED NEPHRITICS WITH ACIDOSIS

- DATA COVERING 10 MONTHS
- " " 12 "
- " " 5 DAYS
- " " 6 WEEKS
- " " 8 "
- SINGLE DETERMINATION
- " "
- " "
- " "
- DETERMINATIONS ON CONSECUTIVE DAYS

CHART VIII

In suppurative and toxic nephritis similar factors operate in the production of acidosis and produce similar results, but it should be emphasized that in acute pyelitis, alkalosis, the result of vomiting of hydrochloric acid, is frequently encountered.

All acid-base balances observed before treatment of such children are plotted in Chart VIII.

When obstruction to the outflow of urine from the tubules is present because of congenital or acquired anomalies, including crystal or stone blockage, acidosis seems to develop first because of failure of reabsorption of sodium. It seems probable that intratubular pressure affects the function chiefly of the distal convoluted tubules, where normally the alkaline glomerular filtrate is converted into acid urine by reabsorption of sodium and substitution of hydrogen arising from carbonic

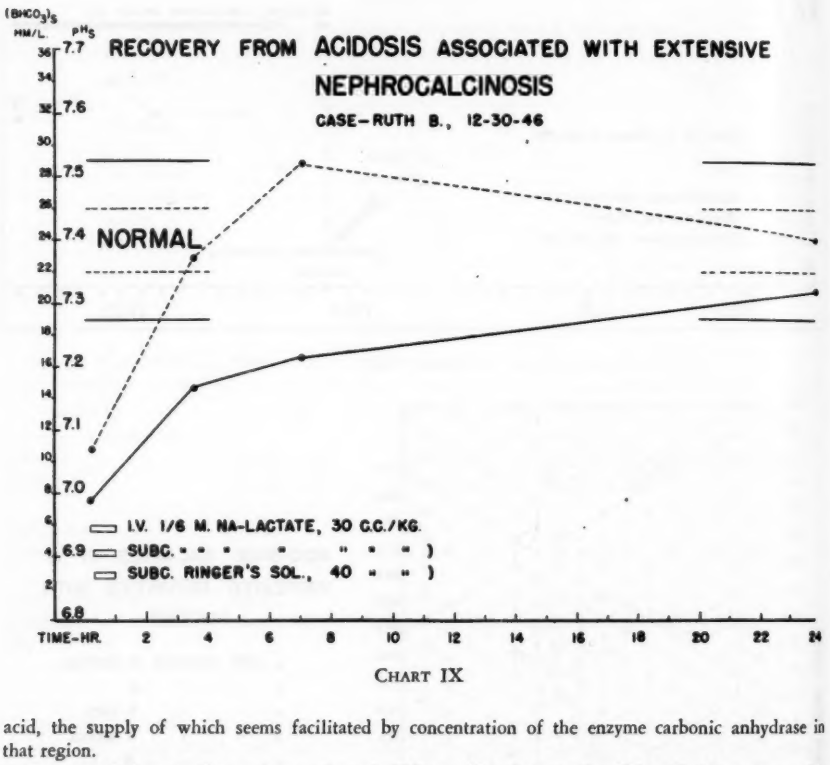

(BHCO3)S MM/L.
pHS
RECOVERY FROM ACIDOSIS ASSOCIATED WITH EXTENSIVE NEPHROCALCINOSIS
CASE-RUTH B., 12-30-46
NORMAL
I.V. 1/6 M. NA-LACTATE, 30 C.C./KG.
SUBC. " " " " " " ")
SUBC. RINGER'S SOL., 40 " ")
TIME-HR.

CHART IX

acid, the supply of which seems facilitated by concentration of the enzyme carbonic anhydrase in that region.

In congenital anomalies such as polycystic kidneys, disturbances of acid-base balance occur with ease and have been reported in detail. They are caused by insufficient normally functioning renal substance.

Another type of congenital anomaly of interest has recently been observed in siblings, the older of whom reached the age of four years and the younger two years before death. In each the primary fault was bilateral renal hypoplasia. The older child, a boy, showed typical renal dwarfism and first presented himself with severe acidosis precipitated by acute respiratory infection. Terminally a pyelo-nephritis with abscess formation was superimposed on the developmental hypoplasia. His younger sister showed only hypoplasia.

Still another type of acidosis can be seen in young infants, which at first is strongly suggestive of renal pathology, but which later can be shown to be due to adrenal cortical insufficiency. Such an infant has been previously described in detail. Several similar cases have since been encountered, and response to desoxycorticosterone has been most satisfactory. Such infants seem to be just one type of

adrenal insufficiency, which involves chiefly tubular function and which persists for a while beyond the neonatal period normally reduced renal function.

Treatment: In extreme or severe degrees of acidosis parenteral alkali administration is indicated, and Na-lactate should generally be given in much the same way that it is given in diarrheal and diabetic acidosis. If edema is absent, and especially if dehydration is present, isotonic (1/6 molar) Na-lactate had best be given. Dosage again depends more upon the initial serum pH than any other factor, but there is usually no strong tendency for immediate recurrence of acidosis as in the case of unchecked diarrhea and no tendency for over-correction as in the cases with much accumulation of lactic or ketone acids. Ten mM/kg. (60ml. 1/6 molar) is usually a quite satisfactory initial dose. If edema is present it has been our practice to give a similar dose in more concentrated solution (one-third to one-half molar) so as to avoid excessive water administration. Such hypertonic solutions should be given intravenously quite slowly or in divided dosage. Hypochloridemia, if present, demands also administration of Ringer's solution, both to correct chloride deficit and to prevent chloride-deficit alkalosis from developing in the event of over-administration of alkali. Hypoproteinemia may also require correction by administration of concentrated serum albumin in order to achieve maximal renal function.

In mild degrees of acidosis, especially when failure of tubular reabsorption of sodium tends toward the development of a persistent $BHCO_3$ deficit, Na-lactate or other alkali may be administered orally. It has been our practice to administer molar sodium lactate added to milk or fruit juice. To prevent recurrence of significant degrees of acidosis we have found that from 1 to 5 ml. of molar Na-lactate per kg. body weight were usually needed daily (Chart VII). Such a procedure as this, of course, may be likened to the feeding of a diet with sufficient alkaline-ash to offset the tendency toward acidosis.

When acid retention contributes significantly to the acidosis, some good may follow restriction of salt in the case of chloride retention, and the feeding of calcium carbonate or calcium lactate when there is abnormal phosphate retention. The latter procedure merely leads to diminished absorption of phosphate from the intestine, because of the phosphate binding effect of calcium which is only partially absorbed, and thus leads indirectly to diminution of plasma inorganic phosphate. In addition, feeding of large amounts of calcium in this way tends to some extent to compensate for the tendency toward a negative calcium balance usually noted in such cases.

In cases of terminal nephritis such treatment is of necessity only palliative and at its best tends only to prolong life. When, however, renal insufficiency is on the basis of reversible change, such as that produced by injury, obstruction or infection, effective treatment of severe acidosis may be life saving and permit eventual complete recovery of the patient.

In infants with a renal type of $BHCO_3$ deficit acidosis on the basis of adrenal insufficiency occasionally huge doses of alkali may be needed to prevent recurrence of acidosis if no desoxycorticosterone is administered. In one case previously reported about 20 ml. molar Na-lactate/kg. were required daily, and I have since heard of a case requiring approximately 40 to 50 ml. With the use of desoxycorticosterone, it has been our experience that alkali can be administered in steadily diminishing dosage and finally dispensed with entirely.

Acidosis Accompanying Severe Infection or the Moribund State: As may be noted from Table III, it is not uncommon to find acidosis associated with acute infections. In infections such as pneumonia, tracheobronchitis, severe tonsillitis, etc., the acidosis, when encountered, was usually mild, and its severity incidence is:

Extreme	1
Severe	3
Moderately severe	14
Mild	47
Total	65

It is possible that in some cases considered mild acidosis a mild CO_2 deficit type of alkalosis with compensation may really have been present, because pH determinations, not often made, would be necessary for differentiation. The point is more of academic interest than of clinical significance since neither change would demand specific measures of treatment, and with recovery from infection spontaneous recovery from the change in acid-base balance would be expected.

In a number of instances, however, the acidosis was severe or extreme and thus became an

important complication affecting the prognosis, and demanded prompt and effective treatment. As a rule a number of factors are responsible for the development of such acidosis, the most important of which are: (1) toxemia leading to tissue injury and altered metabolism and particularly to liver damage with resultant ketosis; (2) dehydration and oliguria, resulting from excessive water loss from evaporation of water from lungs and skin, from diminished fluid intake, or from concomitant vomiting and diarrhea; (3) convulsions leading to excessive lactic acid production; (4) circulatory failure; and (5) starvation leading to ketosis and preventing proper restoration of water and minerals lost from the body.

When actual sepsis existed and had led to an apparently moribund state, the degree of acidosis was frequently more marked. The severity incidence is:

Extreme	8
Severe	16
Moderately severe	20
Mild	33
Total	77

The pathogenesis of this type of acidosis is similar to that of the acidosis of severe infection and is usually complex. Circulatory and renal failure play relatively more important roles. Prompt recognition and institution of effective therapy of the more severe degrees of acidosis in this category have become increasingly important with the availability of the newer sulfonamides and antibiotics for the treatment of infection.

Treatment follows the principles and details already discussed for other types of acidosis.

Miscellaneous Types of Acidosis: From Table III the diversity of the causes of acidosis grouped under the above heading can be noted, and the clinical pictures and proper indicated treatment usually are easily deduced. A few types, however, deserve special consideration.

Acidosis of Salicylate Intoxication: Severe acidosis from this cause is to be expected chiefly in infants and young children, who seem more easily poisoned than do older children or adults. The pathogenesis of changes in acid-base balance of salicylate intoxication seems to be as follows: There first may occur primary hyperventilation, without much else noted in the way of symptoms, which leads to CO_2 deficit alkalosis. Compensatory excretion of $BHCO_3$ into the urine follows, producing some degree of deficit in the blood and body fluids. Then ketosis developes and becomes intense and results in an acidotic type of $BHCO_3$ deficit which may reach a severe degree. The incidence of severity is:

Extreme	1
Severe	8
Moderately severe	11
Mild	4
Total	24

The degree of acidemia (fall in plasma pH) is usually relatively slight, because hyperpnea tends to be extreme. Four separate factors seem to contribute to such extreme hyperpnea: (1) primary stimulation of the respiratory centre which precedes acidosis and often persists after successful treatment of it; (2) acidemia; (3) fever, often high; and (4) frequent absence of serious disease of debilitating factors in the infants and children receiving the drug. Despite the favorable aspect of such relatively mild acidemia, full dosage of Na-lactate is usually required to effect complete correction of the acidosis, because ketosis cannot be abolished as quickly as in diabetic acidosis. In some infants it seemed as if ketosis persisted as long as salicylate remained in the body, despite the antiketogenic effects of lactate and glucose administration. The rapid loss of glycogen from the livers of animals administered salicylate is suggestive of disturbance of the glucose $\rightleftarrows$ glycogen cycle, and perhaps there is poisoning of enzymes by salicylate which results in severe and persistent ketosis. There is some suggestion in our studies that unusually large amounts of glucose with added insulin tend to reverse this situation. Insulin, however, must be administered with caution because of the tendency for spontaneous hypoglycemia in salicylate intoxication.

Other manifestations of salicylate poisoning, particularly the hemorrhagic tendency associated with hypoprothrombinemia, may be just as important as the acidosis, and demand treatment.

Sulfanilamide Intoxication: From the early work of Southworth, who demonstrated that the urine became alkaline following administration of sulfanilamide; of Hartman, Barnett and Perley, who showed that (as in salicylate intoxication) primary stimulation of the respiratory center, often with CO_2 deficit alkalosis, was one of the early effects of sulfanilamide which could not be explained by the production of methemoglobinemia; and the more recent observations of Pitts on the renal mechanism of acidification of the urine, it now seems evident that sulfanilamide tends simultaneously to cause acidosis by poisoning carbonic anhydrase in the distal convoluted tubules, which leads to

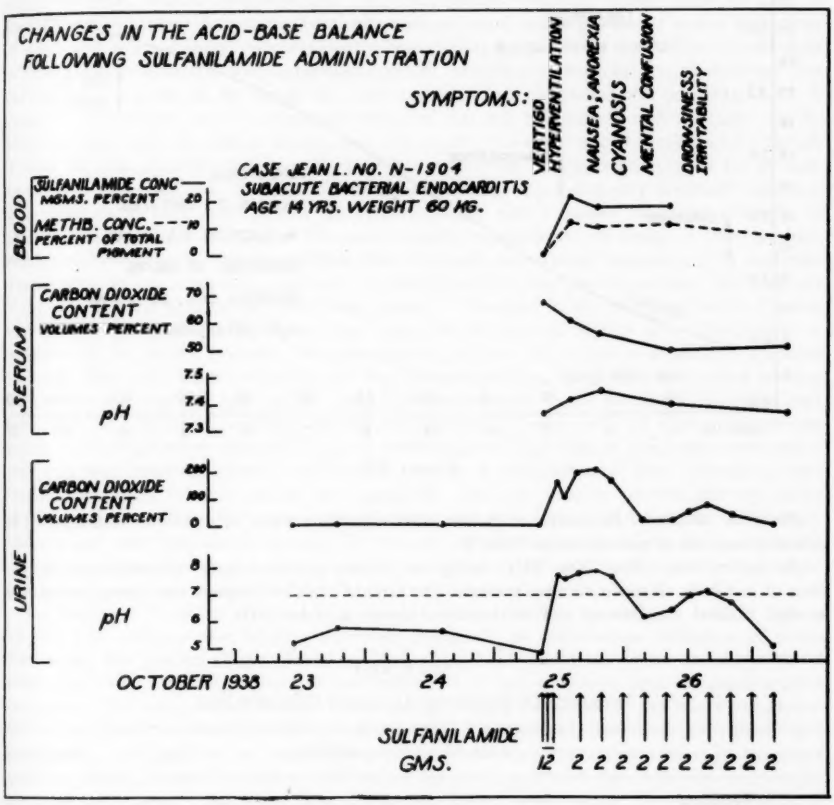


CHART X

failure of Na reabsorption and H^+ ion excretion, and alkalosis by stimulating hyperventilation. The latter condition generally is seen first and then compensated for and occasionally may be followed by acidosis, especially if there are any other factors also operating in favor of $BHCO_3$ reduction. We have, however, never seen acidosis produced by sulfanilamide alone which was characterized by $BHCO_3$ reduction to the zone even of moderate severity.

Snakeroot (Milkweed) Poisoning: One of the most interesting of the cases of miscellaneous acidosis was due to poisoning resulting from ingestion of milk obtained from cows eating snakeroot (Eupatorium urticaefolium). Mention of this case was recently made in a study of diabetic acidosis and other types of acetone body acidosis. In this case, ketosis was persistent (Chart XI) and response to administration of large amounts of Na-lactate and glucose quite slow.

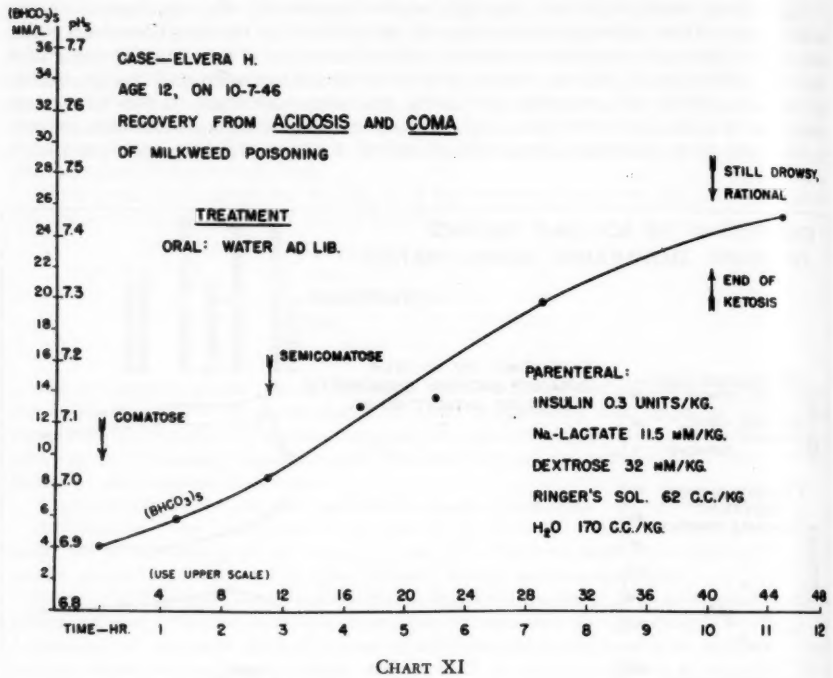


CHART XI

Metabolic Alkalosis: For purposes of later discussion the severity of metabolic alkalosis will be in accord with the scheme shown in Table II.

As may be noted from Table VIII, during the 24 year period of study, 1923-46 inclusive, 363 cases of metabolic alkalosis were encountered. The ratio of acidosis/alkalosis was approximately four to one. Clinical classification and incidence are shown in Table VIII.

TABLE VIII

INCIDENCE OF METABOLIC ALKALOSIS 1923–1946 INCL.

	1923–33		1934–46		Total		Percent
I. Vomiting	61	+	103	=	164		45.2
A. Obstructive	41	+	94	=	135		
1. Pyloric	33	+	78	=	111		
2. Intestinal	8	+	16	=	24		
B. Non-Obstructive	20	+	9	=	29		
II. Alkali Administration	35	+	132	=	167		46.0
A. Accidental	22	+	48	=	70		
B. Intentional	13	+	84	=	97		
III. Other Causes	11	+	21	=	32		8.8
			Total		363		100.0

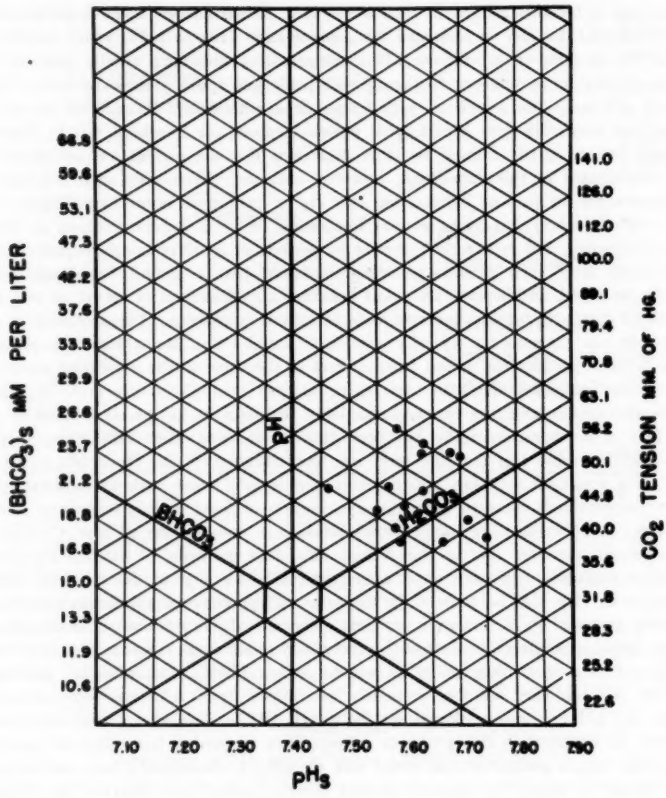
Obstructive Vomiting: In this group there were 135 cases, 111 of which were congenital hypertrophic pyloric stenosis, and 24 intestinal obstruction or fistula. Although the diagnosis of alkalosis in these cases was not established with certainty until the carbon dioxide content of the blood serum was determined, there were usually a number of important clinical symptoms or findings which indicated the existence of alkalosis. As in acidosis, respiration is alone one of the most important clinical symptoms. When alkalosis is of the metabolic type, respiration tends to be compensatory in the sense that it becomes altered in such a way that carbon dioxide tends to accumulate in the blood and to prevent decrease in hydrogen ion concentration (rise in pH), which would otherwise follow upon the increase in bicarbonate. This compensatory breathing usually takes the form of shallow, slow respiratory movements, frequently with prolonged apneic pauses and with a rhythmicity of depth and rate ordinarily associated with Cheyne-Stokes breathing. In many of the infants with extreme alkalosis associated with hypertrophic pyloric stenosis, the breathing was so depressed that one frequently had to satisfy himself by close inspection that the patient was breathing at all. It should be remembered in this connection, however, that not infrequently such a patient may be disturbed, particularly by pain or hunger, and may cry or have more normal ventilation for periods of time. In such instances this more normal respiration really is hyperventilation as far as compensation is concerned, and is usually followed by periods of more obviously depressed breathing. It is particularly after such periods of hyperventilation that a second important symptom of alkalosis may be noted, i.e., tetany. The most common manifestations of tetany of this type have been generalized muscular rigidity, together with occasional convulsions. Laryngospasm is also occasionally seen. In our experience a typically positive Chvostek's sign has seldom been present. Color of the skin in these patients has varied from normal to slate-gray in the present of severe dehydration. Despite the prolonged apnea in some cases, marked cyanosis is very rare. This perhaps is explained by the greater tendency for oxyhemoglobin to retain its oxygen as a result of increased alkalinity. The urine characteristically has been concentrated and acid. This unexpected reaction probably results from the fact that the total base concentration of the blood has invariably been diminished, as a result of vomiting, and the excretion of acid urine with its minimal bicarbonate content is a compensatory measure as far as conservation of fixed base is concerned. Ammonia is present in large amounts, another compensatory measure in conservation of base. Chloride is characteristically absent, however, and in this respect only does the urine of extreme alkalosis due to vomiting differ markedly from the urine of extreme alkalosis due to diarrhea and dehydration. Albumin and casts may also be present. In the cases of hypertrophic pyloric stenosis, aceto-acetic acid has rarely appeared in the urine in amounts sufficient to give positive ferric chloride tests. In the cases of intestinal obstruction, ketosis has been somewhat more frequent.

The highest CO_2 content observed by us was 61 mM/l. ($BHCO_3$ 58 mEq./l.), and the highest pH was 7.78. All acid-base balances accurately determined by simultaneous estimation of serum CO_2 content and pH are shown plotted in Chart XII. While sometimes severe manifestations of tetany were to be observed in this group of infants, it is surprising how often no manifestations were noted. The lowest serum chloride noted was 45 mEq./l. Occasionally very marked concentration of the blood as shown by increased plasma protein content was observed, the highest value found being 9.46 gm./100 cc. serum. Twenty-four hours after the administration of parenteral fluids the plasma protein level fell to 6.47 and on the next day to 5.77. As a rule, however, despite the marked anhydremia, the plasma protein values are within normal limits. The explanation lies in the fact that there has been actual reduction in the total amount of plasma protein because of attendant starvation. Such reduction tends to be masked by anhydremia. This is a significant point. Probably because of the marked oliguria, the nonprotein nitrogen of the blood almost invariably is elevated, occasionally to a marked degree. The highest nonprotein nitrogen observed in the cases of congenital hypertrophic pyloric stenosis was 116 mg./100 ml. blood, while in the group with intestinal obstruction it was 152 mg. These cases did not exhibit ketone acid accumulation. Likewise, lactic acid was not regularly elevated, and in the few instances in which it was found abnormal, the elevation seemed to be merely the result of marked anhydremia. The highest lactic acid value found was 39.5 mg./100 ml. (4.4 mEq./l.).

Treatment: As in severe infantile diarrhea with acidosis, treatment of complications of congenital hypertrophic pyloric stenosis and intestinal obstruction must be on a broad basis. Our present concept of adequate treatment may be outlined as follows:

1. Emergency treatment of alkalotic tetany. If death seems imminent because of absence of

spontaneous respiration following tetanic convulsive seizures and apparent ineffectiveness of artificial respiration, as happened on several occasions in our experience after successful operation, the most effective treatment is administration intravenously of hydrochloric acid. Our experience has been that only a small amount (2 or 3 ml. of approximately 0.01N HCl [which can be made quickly by adding .75 ml. of concentrated HCl—approx. 14N and sterile to 1 l. of sterile Ringer's solu-



INITIAL ACID-BASE BALANCES IN PYLORIC STENOSIS

CHART XII

tion]) has to be administered intravenously to stimulate respiration so that it continues spontaneously. A site for injection should be chosen so that if inadvertently any acid reaches the subcutaneous tissue, the resulting slough will not be disfiguring. With reestablishment of breathing, at first 30% CO_2—70% O_2, later 5% CO_2—95% O_2 should be administered by funnel until 5% $CaCl_2$ can be injected intravenously. Some authorities recommend as much as 3 ml./kg.; as little as .25 to .5 ml./kg. has been sufficient in our experience to control convulsions if more or less complete correction of alkalosis is soon accomplished. Magnesium sulfate, because of its depressant effect on respiration, is contraindicated at this juncture.

2. Relief of Alkalosis. The direct effect of such a small amount of HCl and the indirect effect of the $CaCl_2$ together would decrease slightly the $BHCO_3$ excess in the blood and body fluids, after equilibrium were established. For a more effective reduction isotonic NH_4Cl (1/6 molar) should be added to an equal volume of Ringer's solution if dehydration is present and the mixture given subcutaneously in a dosage of 60 ml./kg. In a few hours an average fall of some 9.1 mM./l. CO_2

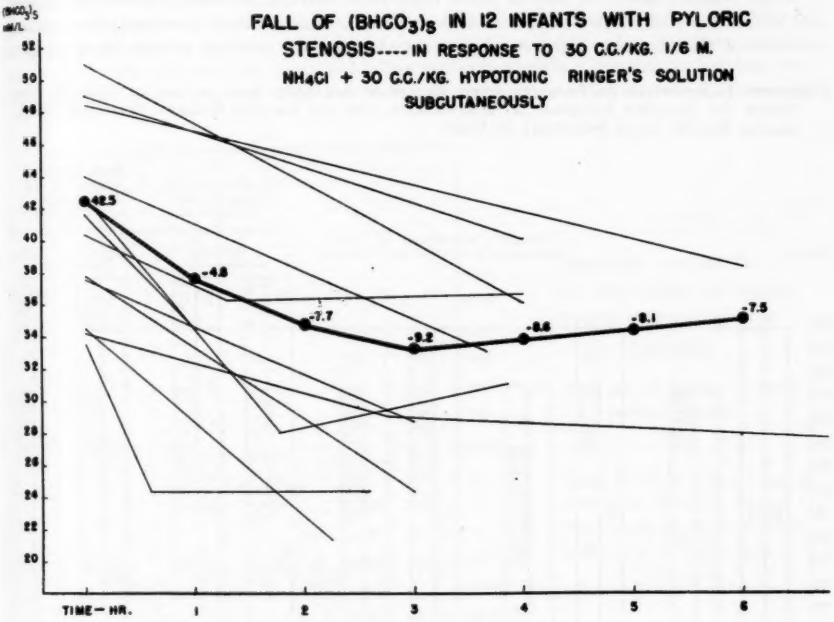


CHART XIII

content (9.2 mM. $BHCO_3$/l.) can be expected (Chart XIII). Liver function is called upon for this effect. For complete relief from alkalosis, restoration of total base, chloride and water in the body fluids, renal activity in response to subcutaneous administration of hypotonic Ringer's solution is called upon (Chart XIV). If oliguria and edema follow such fluid administration because of depletion of plasma proteins, no such correction of alkalosis would be noted until renal activity could be reestablished by transfusion with, preferably, concentrated serum albumin or concentrated plasma.

3. Preoperative Parenteral Feeding. To lessen operative risk because of hypoglycemia or acute protein deficiency, parenteral feeding with D.A.R. administered subcutaneously after correction of dehydration and hypoproteinemia is carried out as in the early management of severe diarrhea.

4. Operative correction of pyloric stenosis. (Fredet-Ramstedt).

5. Post-operative Feeding. As previously described.

Non-Obstructive Vomiting: When severe vomiting is not on the basis of obstruction in the gastro-intestinal tract, alkalosis is much less common. "Cyclic" vomiting, for instance, is one of the chief contributors to the type of acidosis included under the heading "nondiabetic ketosis." The reason seems to be the fact that most nonobstructive causes for vomiting are infections which so reduce the gastric acidity that often there is no free hydrochloric acid present. One notable exception is pyelitis. Pylorospasm with maintenance of gastric secretion of hydrochloric acid is likely to be associated with acute urinary tract infection and alkalosis frequently results. The meningismus of pyelitis frequently is due to alkalotic tetany. It is important to realize that the urine in such

instances is likely to be acid, as in pyloric stenosis with alkalosis, and alkali administration may fail to alkalinize it, while administration of sodium chloride will. This point is again assuming importance in view of the fact that effective streptomycin therapy requires an alkaline reaction of the urine.

Treatment follows the principles which apply to the treatment of alkalosis resulting from obstruction of the gastro-intestinal tract.

Alkali Administration: As may be noted from Table VIII alkalosis resulted both intentionally and accidentally from alkali administration. A condition of mild alkalosis is necessary for continued secretion of alkaline urine which may be desired to reduce the tendency of sulfonamide drugs to

SCHEMATIC ILLUSTRATION OF RECOVERY FROM METABOLIC ALKALOSIS DUE TO LOSS OF GASTRIC JUICE WHEN (1) RINGER'S SOLUTION IS ADMINISTERED, AND (2) LACTATE-RINGER'S SOLUTION (PHYSIOLOGIC BUFFER SALTS SOLUTION) IS USED.

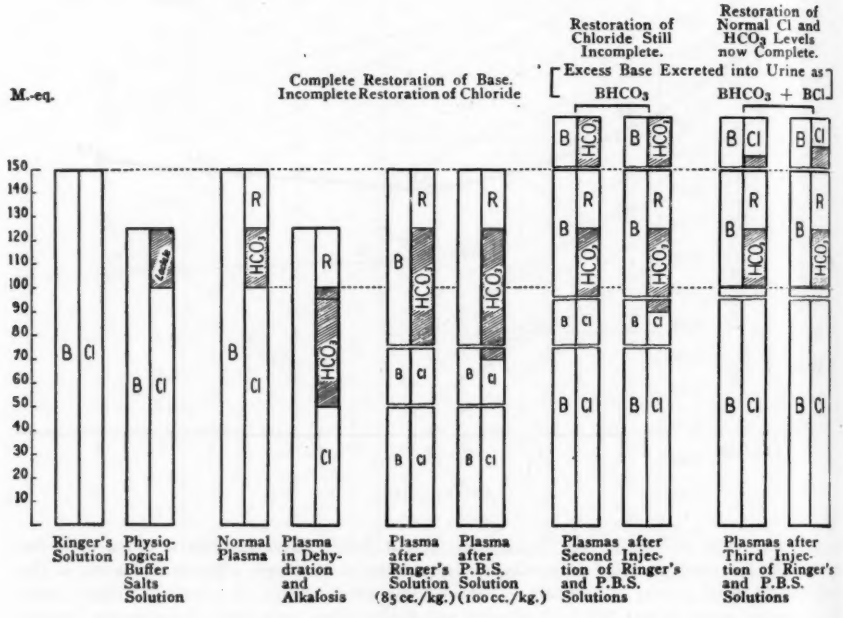


CHART XIV

precipitate in the urinary tract in sulfanilamide or streptomycin treatment of urinary tract infections or in treatment of hemoglobinuria such as accompanies transfusion reaction.

Under the heading of accidental alkalosis were included (1) all cases of overtreated acidosis and (2) all cases of intentionally produced alkalosis that went beyond the zone of mild or moderate degree. The most common mistake was first to treat diarrheal acidosis in a young infant as outlined previously and then to administer the amount of Na-lactate needed for the older child to maintain urine of high alkalinity in the presence of sulfonamide chemotherapy—5 ml. molar/kg./day—before it was realized that such young infants' kidneys could not clear sodium that rapidly. In fact, it often is impossible in any way to stimulate secretion of highly alkaline urine in such young infants, and 2 ml./kg./day of molar Na-lactate is as much as can be given safely. Contributing some to the unwanted alkalosis seen sometimes in such infants was the oliguria which followed too much sodium chloride administration leading to edema. Such was especially true if hypoproteinemia was allowed to persist.

The second most common mistake was failure to correct hypochloridemia during treatment of acidosis. Again the mistake occurred chiefly in young infants—especially those thought to have

some degree of adrenal insufficiency—where chloride excretion into the urine sometimes occurred with subnormal plasma chloride concentration.

Less frequently alkalosis was produced accidentally by treatment of presumptive acidosis that later was found not to exist, and in treatment of children with severe renal insufficiency on an organic basis who were incapable of secreting highly alkaline urine.

Miscellaneous Types: In this group fell mostly cases of mild alkalosis for the development of which no good cause could be ascertained, and for which specific treatment was not needed. Specific mention, however, should be made of effects of fibrocystic disease of the pancreas. Despite the tendency for chronic diarrhea, alkalosis and not acidosis tends to develop. We have seen five such examples, two extremes, the others mild. The explanation seems to be that the alkaline component of mixed gastro-intestinal juices contributed by the pancreas is lacking, and the failure of

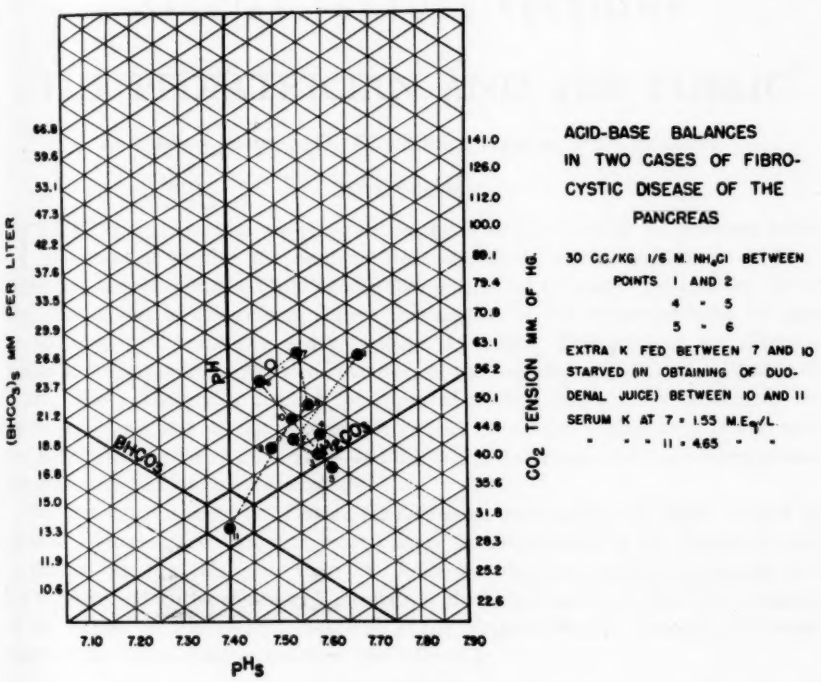

ACID-BASE BALANCES
IN TWO CASES OF FIBRO-
CYSTIC DISEASE OF THE
PANCREAS
30 CC./KG. 1/6 M. NH4Cl BETWEEN
POINTS 1 AND 2
4 " 5
5 " 6
EXTRA K FED BETWEEN 7 AND 10
STARVED (IN OBTAINING OF DUO-
DENAL JUICE) BETWEEN 10 AND 11
SERUM K AT 7 = 1.55 M.Eq/L.
" " " 11 = 4.65 " "
(BHCO3)s MM PER LITER
66.8 59.6 53.1 47.3 42.2 37.6 33.5 29.9 26.6 23.7 21.2 18.8 16.8 15.0 13.3 11.9 10.6
CO2 TENSION MM. OF HG.
141.0 126.0 112.0 100.0 89.1 79.4 70.8 63.1 56.2 50.1 44.8 40.0 35.6 31.8 28.3 25.2 22.6
pHs
7.10 7.20 7.30 7.40 7.50 7.60 7.70 7.80 7.90
BHCO3
PCO2
H2CO3
B Cl
B R HCO3
B Cl

CHART XV

reabsorption (diarrhea) thus tends to reflect more loss of gastric juice. In one of the two cases of extreme alkalosis, a number of simultaneous determinations of pH and $BHCO_3$ were made and the data are plotted in Chart XV. The pulmonary involvement in this infant was not that of the usually disseminated bronchiolectasis but consisted only of partial atelectasis of the right upper lobe. As may be noted, considerable alkalemia always accompanied the $BHCO_3$ excess. In the other case of severe alkalosis a serum pH of only 7.48 was found associated with a $BHCO_3$ of 44.0 mH./l. In this instance, because of extensive chronic bronchiolitis, despite dyspnea characterized by rapid and labored respiration, CO_2 tension remained high enough to effect almost complete compensation for the $BHCO_3$ excess. Without the latter, this patient probably would have had a respiratory type of acidosis as a result of the pulmonary changes. On the other hand the chronic diarrhea of celiac disease tends definitely toward the development of acidosis. Also in this group were two nonspecific types of diarrhea with alkalosis which resembled the infants recently studied by Gamble and

Darrow, with the finding of an altered mineral composition of gastro-intestinal secretions favoring development of alkalosis.

Respiratory Alkalosis: Primary hyperventilation with production of CO_2 deficit alkalosis may be noted in (1) febrile conditions where no great tendency toward acidosis exists; (2) sulfanilamide administration; (3) the early stages of salicylate intoxication; (4) involvement of the central nervous system such as in the early stages of meningitis or as a residual manifestation of encephalitis; (5) hysteria; and (6) the early recovery phase of acidosis relieved by alkali administration. As a rule, there are no definite clinical manifestations, but because of the ever present danger of tetany and circulatory failure, treatment with CO_2—O_2 inhalation must be quickly available. Such treatment has proved easier and more effective than attempts at respiratory depression.

Pediatrics

VOLUME 2 NOVEMBER 1948 NUMBER 5

SPECIAL FEATURE SECTIONS

THE PEDIATRICIAN AND THE PUBLIC

EDWARDS A. PARK, M.D., *Editor*, PAUL HARPER, M.D., *Associate*

INTRODUCTION

THREE communications are presented in this issue all of which are pertinent to the discussion of whether the Academy shall support the recommendation of its Committee for Improvement of Child Health that federal aid be sought for pediatric education. The editors of this column believe that support of this recommendation or some modification is of immediate and paramount importance. This position was ably presented in the statement by Maryland members of the Academy of Pediatrics. (PEDIATRICS 2:222, 1948.) The public demand for improved medical care will not be denied. The profession must lead in this program or be led. The most urgent need is for more and better training for all physicians—and this is also the area in which agreement among the profession should be most complete.

The first letter is from Dr. Donald G. Anderson, Secretary of the AMA Council on Medical Education and Hospitals, and presents the official view of the Council. It may be pointed out that this letter from Dr. Anderson indicates a legitimate change since the statement which he signed as a member of the Subcommittee on Medical Personnel of the Section on Professional Personnel at the National Health Assembly. The statement of this subcommittee contained the following:

". . . There is evidence to indicate the local support will be insufficient to meet the financial needs of a sound and expanding program of medical education, and that some form of federal support will be necessary. Federal appropriations should entail no federal control of the administration, curriculum and student admissions of the medical schools. . . ."

The second communication is from Dr. Allan M. Butler, Professor of Pediatrics at Harvard Medical School, which reviews the changing positions of the AMA with regard to medical care.

The final communication is from Dr. Paul Hawley, Chief Executive Officer, Blue Cross—Blue Shield Commissions. Dr. Hawley emphasizes the urgent need for the profession to take the lead in providing improved medical care to forestall the rising demand for socialized medicine. He makes the point that the profession in the recent past has not exercised such leadership and that time is running out. This speech by Dr. Hawley was presented before the American Medical Association during the meeting in

June in Chicago. The editors of this column feel that the profession should be fully informed of facts and expressions of opinions on both sides of the controversy. It is in the spirit of fairness and open-mindedness that Dr. Hawley's views are presented in the column. The original speech has been slightly shortened with Dr. Hawley's permission because of space limitations.

July 29,1948

DEAR DR. HARPER:

The present attitude of the Council on Medical Education and Hospitals with respect to federal support for pediatric education is set forth in the following action taken by the Council in June, 1948:

"The Council has gone on record favoring an intensive effort to secure voluntary support for medical education. Therefore, the Council is opposed to the plan of the American Academy of Pediatrics (for federal support of pediatric education). The Council feels that it is extremely unwise for one specialty in medicine to seek federal aid before medicine and medical education in general have approved this principle."

Recent discussions with other groups and individuals concerned with the financial support of medical education have encouraged the Council to believe that the possibilities of securing adequate support for medical education from voluntary sources are far from exhausted. A concerted effort to obtain such support appears feasible and the initiation of such a program is being very actively considered.

The more closely the Council has studied the problem of federal support of medical education, the more clearly it has appeared that direct federal support on any significant scale cannot be provided without opening the door to federal regulation of the medical schools. This conclusion appears inescapable if account is taken of the basic principle that the federal government cannot appropriate funds to institutions over which it has no control. At the moment, it seems exceedingly doubtful that legislation could be framed that would insure that federal appropriations would entail no federal control of the administration, curriculum, and student admissions of the medical schools. While federal regulation might be minimal initially, it does not appear that adequate safeguards could be established guaranteeing that the control would not be tightened in the future. It seems clear that once the medical schools made commitments based on federal support of any substantial character, the schools would find it difficult and probably impossible to decline such support in the future, even if the terms on which it was offered were not satisfactory.

There are other cogent reasons why the Council is hopeful that federal support will not be necessary at this time, but to review them all is beyond the scope of a letter.

You may be interested to know that a few months ago a group of medical educators, acting in the belief that federal support might be necessary and that satisfactory legislation could be formulated if medical educators took the initiative, volunteered to assist in preparing a bill to provide federal support of medical education. This group was almost immediately disillusioned as to the extent to which its views regarding the form such legislation should take would be respected.

A few months ago a number of medical educators appeared to be resigned to the fact that federal support of medical schools was inevitable. Today there is a growing conviction that an all-out effort should be made to secure adequate support from private sources

before turning to the federal government to pay us out of our difficulties. As one educator has put it, "If the independence of the medical schools is worth anything, it is worth working and fighting for."

I believe that the Council would fully agree with you that any nation-wide program for securing increased support for medical education should not be limited to education in any one specialty.

(signed) DONALD G. ANDERSON

August, 1948

DEAR DR. PARK:

Several people, including both those who endorse and those who oppose such federal support of pediatric education as recommended by the Executive Board of the Academy have asked me about the recommendation of the AMA's Council on Medical Education and Hospitals which was approved by the House of Delegates of the AMA at its recent meeting in Chicago in June.

Dr. L. J. Henderson in discussing a physiologic response frequently remarked it was "as might have been expected." The Council's recommendation is an orthodox AMA response. The first sentence concisely reiterates the AMA's faith in the adequacy of voluntary contributions or charity. Perhaps incidentally, it suggests that deans and university presidents have not made the desired intensive effort to obtain adequate voluntary support for medical education. We all hope as stated in the subsequent resolution passed by the Academy's Executive Board in Milwaukee that "a national foundation, the purpose of which is to secure contributions from the general public for the support of medical education," is successful in meeting "the financial needs of medical education."

> "Together let us beat this ample field,
> Try what the open, what the covert yield:
> The latent tracts, the giddy heights, explore
> Of all who blindly creep, or sightless soar;"

for as Pope writes a few lines later: "Hope springs eternal in the human breast."

But we can all subscribe to the faith which the Executive Board seems to imply by saying, "this action on the part of the AMA should accomplish the same ultimate objective regarding medical education as contained in the recommendation of the Committee for Improvement of Child Health"? Once again Pope's lines come to mind.

> "In Faith and Hope the world will disagree,
> But all mankind's concern is Charity."

The second sentence of the AMA's recommendation consistently follows its usual policy by emphatically saying "what not to do." The third sentence reflects the AMA's tradition that unanimity is a prerequisite to wise action.

I am sure our Executive Board appreciated that some such response was to be expected. As Oliver Garceau remarks in his excellent book on the American Medical Association,* "A large federate association is inherently sluggish and bound by traditional attitudes." It also appreciated the unpredictable delay that would have resulted in making Academy action contingent upon AMA approval.

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* The Political Life of the American Medical Association, Harvard University Press, Cambridge, Massachusetts, 1941.

Mr. Baruch speaking last November to the County Medical Societies and Hospital Association of New York City said:

"Even the least ambitious schemes for improving the nation's health require more doctors, all competently trained. Why aren't more doctors being educated?"

In studying that question, I was struck by how expensive training a doctor has become—in dollars and in time. . . .

"In the matter of adequate medical care, too many doctors have been fighting a rear-guard action too long. I feel I must warn those doctors—time is running against them. The medical profession has justly earned great influence in the community. It can keep that hold only as it moves forward. It will lose that hold if it has nothing but objections to offer, if it has eyes only for what not to do."

"We must look for what can be done—and do it."

"The great question is how? I do not want to seem to say I know the answers. We do know the public is demanding better and more medical service through some action—political or otherwise."

The New York Academy of Medicine's report on "Medicine in the Changing Order" states:

"There seems no alternative other than government aid if educational standards are to be raised or even maintained. . . . If medical schools are to continue as centers of research . . . here also government aid may be necessary."

In your speech before the New York Academy of Medicine a year ago this spring, published in the Journal of Pediatrics, you set forth some simple facts about the economics of medical education that demand action including the following: "With the shrinking resources and the disappearance of the old private supports and without the addition of new, the full time medical schools cannot continue." In this connection isn't it odd that those who would have us rely most on private support seem least concerned about the dissipation of private capital by war and inflation.

The commendable tolerance of the AMA's statement in comparison with previous ones on somewhat similar occasions deserves emphasis. In 1934 when the Board of Regents of the American College of Surgeons promulgated a prepayment plan for medical care at approved hospitals, the AMA House of Delegates immediately demanded that its members appear before the Board of Trustees and Judicial Council to explain and justify the reasons for this independent action by a specialistic organization. Many will also recall the JAMA's editorial castigation of the Committee of Physicians when it in 1937 presented certain principles and proposals for improving medical care. The vehemence of the comments in relation to the conservatism of the proposals is amusing and informative enough to warrant quoting both the proposals that pertained particularly to financing medical education and Dr. Fishbein's comments.

Proposal 3: "That public funds should be made available for the support of medical education and for studies, investigations, and procedures for raising the standards of Medical practice. If this is not provided for, the provision of adequate medical care may prove impossible.

Proposal 4: "That public funds should be available for medical research as essential for high standards of practice in both preventive and curative medicine.

Proposal 5: "That public funds should be made available to hospitals that render service to the medically indigent and for laboratory and diagnostic and consultative services."

The statement which accompanied the above ended with the following opinion:

"The medical profession should initiate any proposed changes because physicians are the experts upon whom communities must depend. Unless the medical profession is ready to cooperate with these other groups they cannot expect to play successfully the part which they should play, nor can they expect to enlist the sympathetic understanding of legislative bodies.

"It seems to us probable that certain alterations in our present system of preventing illness and providing medical care may become necessary; indeed certain changes have already occurred. Medical knowledge is increasing rapidly and is becoming more complex. Changes in economic and social conditions are taking place at home and abroad. Medicine must be mobile and not static if medical men are to act as the expert advisors of those who convert public opinion into action."

"The condition is general that action should be taken only upon the basis of demonstrated need and as experience accumulates to indicate that such action is likely to attain its ends in a nation compromising forty-eight States in which climatic, economic and social conditions vary greatly."

Said Dr. Fishbein (Minnesota Medicine 20:795, 1937):

"The action of the men who thoughtlessly lend their names to the project is worse than questionable. In Russia, and in the United States, if the 430 signers (of the proposals) have their way, all matters relating to the distribution of Medical care, are to be in the hands of experts.' "

And again editorially (JAMA 109: 1280, 1937):

"It should not be necessary to point out again in the Journal the danger of federal subsidies for medical schools. . . . The danger of putting the government in a dominant position in relation to medical research is apparent. . . . Still more serious is the fifth proposal, to the effect that the government subsidize private hospitals. . . . The tender of government funds to such institutions . . . appeals to the unthinking physicians who have endorsed these principles and proposals. Certainly the unthinking endorsers of the . . . principles owe to the medical profession some prompt disclaimers."

These comments, according to Dr. Roger I. Lee, reflected the attitude of the Trustees of the AMA as well as of Dr. Fishbein.

As you know, a few years later the same individuals were advocating a National Science Foundation, which would provide federal support to medical research, the Hill-Burton Hospital Construction Act, which would give grants-in-aid to private hospitals, and the Taft National Health Act of 1947, which states "that it is the policy of the United States to aid the states, through consultative services and grants-in-aid, to make available medical, hospital, dental and public health services to every individual regardless of race or economic status."

Dr. L. H. Bauer and Dr. Elmer Bagnall have criticized reference to such past history, claiming that it is no longer pertinent. Reference is not made here nor has it been made with narrow malice. It is made because, "by their fruits ye shall know them," and cognizance of past behavior may possibly permit better appraisal of the wisdom of present judgements. Even if such reversal of opinion indicates courageous and praiseworthy admission of error, it demonstrates lack of vision. How convenient if we could all avoid responsibility for past mistakes. Garceau comments that, "The whole record is of a politically very skillful rear-guard action." But he then adds, "Undoubtedly much of this change was a normal response of the group to external pressure, to the steady degenerating state of its public relation." Mr. Raymond Rich, after studying the AMA as its public relations council, suggested that the difficulty was partly due to a greater concern for the profession's rather than the public's interest.

Mr. Baruch, as quoted above, makes quite clear what he thinks will be the result of such rear-guard tactics. You in the address already referred to remark, "In this critical period of change, when the handwriting appears on so many walls, the behavior of organized medicine is humiliating, and its leadership has seemed incredibly stupid." Certainly

the record is not unlike that of Joe Martin; namely, ineffectual negative votes against all measures to meet changing circumstance and yet Martin enjoys the continued support of many people. I suppose the explanation is that many people just don't want to face the reality of changing circumstance.

The record of the AMA in this respect is so striking in its consistency that it deserves recording, if only in such outline form as can be set forth by one on vacation without the benefit of a reference library.

We might start by recalling that raising the standard of medical education was initiated by such men as Welch and Abraham Flexner against considerable opposition. Indeed full-time salaried clinical teachers have been opposed by "organized medicine" until very recently. Yet today the AMA takes credit for the improved standards of medical schools.

The Millbank Funds inquiry into medical care in up-state New York in the late 1920's, was bitterly opposed by the AMA. Yet 10 years later an editorial in the JAMA praised the Commonwealth Fund's rural health project.

The industrial medical service of the Endicott-Johnson Company was denounced in the JAMA, 1928-1932. I'm sure it is approved today.

The Blue Cross type of hospital insurance which has been expanding since 1929 was opposed by the AMA as late as 1934. Since about 1937 it has been enthusiastically endorsed.

The inception of almost every prepayment medical service in the United States, except those organized by state medical societies, was opposed by "organized medicine." Among such, with approximate dates of opposition as I remember, are: The Trinity Hospital Insurance Plan, Little Rock, Arkansas, 1939; United Medical Service, Chicago, 1932; the Ross-Loos Clinic, Los Angeles, 1934; Michigan State Medical Societies' initial program for insurance medicine, 1934; Elk City Cooperative Hospital, Oklahoma; The White Cross, Boston, 1938; Chicago University Clinics; Group Health Association, Washington, D.C., 1938; The Permanente Foundation Health Services, 1946; The Health Insurance Plan of New York City, 1946-48. The degree of opposition varied from subtile to overt hostility, but there can be no doubt about there having been opposition. This seems short sighted for it appears that conservative wisdom would have encouraged a multiplicity of voluntary endeavor to find ways to solve the difficult problems inherent in voluntary prepayment medical plans. The AMA may finally have recognized this fact, for at the National Health Assembly in Washington this spring it agreed that voluntary prepayment schemes should not be limited to those of state medical associations.

That the AMA would not view the Academy's survey with enthusiasm also was not unlikely from the scathing denunciations of the following survey studies: Report of the Committee on the Costs of Medical Care, 1932; American Foundation Studies, American Medicine, Expert Testimony out of Court, 1937; Report of Technical Committee on Medical Care, Interdepartmental Committee to Coordinate Health and Welfare Activities, 1938; the California Medical-Economic Survey, about 1937, and fully reported in Economic aspects of Medical Service, by Dodd and Penrose, 1939; Interim report on Wartime Health and Education, Subcommittee U.S. Senate 1945.

Finally the AMA has opposed almost all federal legislation pertaining to the financing of medical care. My memory goes no further back than opposition to the Sheppard-Towner Act from 1928-1932. Since that time it has opposed the Farm Security Administration Medical Programs, 1937; the original Wagner-Murray-Dingle Bill, 1939, and the

subsequent revisions; Senator Pepper's Maternal and Child Health Bill, 1945; Emergency Maternal and Infant Care Program, 1944; and Senator Saltonstall's School Health Services Bill, 1947.

This record of opposition might have been fine if it had prevented the unwanted changes. But certainly such rear-guard tactics as the AMA has engaged in have neither met the public's needs nor protected the doctor in the present changing economic order. While the AMA has denounced all these measures, the public has enacted and the AMA has accepted (1) government financing of hospital construction on a national basis; (2) government financing of medical education and medical research by grants from the Federal Security Agency and the proposed National Research Foundation; (3) government extending its support of maternal and child care through the Children's Bureau of the Federal Security Agency; and (4) government extension of public health services. The AMA has also, in endorsing the Taft National Health Act of 1947, approved government financing of medical care for low income groups. Incidentally the acceptance of these five things means that the AMA has tacitly endorsed five of the six parts of the original Wagner-Murray-Dingle Bill which considering the bitter denunciation of this bill for eight years is indeed noteworthy.

In view of the fact that perhaps half the budgets of medical schools and half the sums expended in medical research are provided by government, Dr. Black's intolerant blast against the Academy's I.C.H. Committee report and the Executive Board's endorsement is somewhat hysterical and beside the point. The Executive Board at its meeting in Chicago this winter wisely refused to be frightened by such a threat. After all, the question before us today is not whether we will or will not have government support for medical education, but rather how will this be accomplished? Will it continue in the more or less haphazard manner by which it has been accomplished up to date or can it be done in a more orderly and coordinated manner?

The latter will require tolerant consideration, reasoned debate and constructive action. Is it not just this that the I.C.H. Committee has initiated and the Executive Board has endorsed? Our Execuive Board deserves praise for appreciating the need of professional leadership. The gracious reply of our Executive Board to the AMA's recommendation should not interfere with the Academy realistically facing the problem of pediatric education and pursuing the Academy's traditional course—constructive leadership—not rear-guard action.

I apologize for the length of this letter, but after all the AMA's record of opposition and "what not to do" is a long one.

(signed) ALLAN M. BUTLER

BLUE SHIELD, OR COMPULSORY GOVERNMENT INSURANCE*

By PAUL R. HAWLEY, M.D.

The dangers that threaten the free practice of medicine in this country are fast becoming critical, and still we delay in uniting in decisive action to meet them.

We waste precious time in quarreling among ourselves over petty questions of local

* A speech delivered at the Conference of Presidents and other Officers of State Medical Associations June 20, 1948.

sovereignty. We amuse ourselves by setting up fantastic straw men, and dissipate our energies in knocking them down, while our enemies have been uniting against us in one national effort. We have thus far done no more than fight a series of rear-guard actions with small unorganized and uncoordinated groups. I know of no more certain road to disastrous defeat.

Our national leaders seem to be purposefully blind to the social changes that are taking place. It is impossible to halt a movement by merely refusing to recognize its existence; and this movement toward extending the benefits of adequate medical care to all of our citizens has already gained too much momentum to be halted by any means. The last hope of American medicine lies in abandoning our present position in the rear of the column, where we have been holding back, and establishing ourselves firmly in the forefront, where we can guide and direct the movement into paths that are the best for our people as well as best for our profession. Too many physicians regard medical care as their exclusive prerogative. We must recognize that the consumer of medical care also has a great stake in it; and, if there has existed any doubt as to this, it should have been dispelled by the deliberations of the National Health Assembly, held in Washington early in May.

I shall offer no defense of the motives that prompted the organization of this Assembly. They may have been, as has been charged, largely political. But however impure the motives, only a very stupid person could have listened to the discussions in the Section on Medical Care and come away unimpressed both by the strength and the determination of the groups committed to an effective program for prepayment of medical care. I emphasize "effective," because the preponderant opinion expressed there was that existing plans are acceptable only so far as they go, that they do not go far enough, and that, if they are to be fully acceptable as a substitute for compulsory government health insurance, the coverage they offer must be extended considerably, and must be uniform throughout the country. In fact, a resolution to the effect that only a compulsory government insurance plan could satisfy these criteria was proposed, and vigorously supported by the American Federation of Labor, the Congress of Industrial Organizations, the Cooperative League of America, the National Cooperative Health Federation, the National Federation of Settlement Workers, the Committee for the Nation's Health, the American Association of Social Workers, the Physician's Forum, the National Counsumers' League, the National Women's Trade League, the United Mine Workers, the American Veteran's Committee, the National Farmers' Union, the Physicians' Committee for Improvement of Medical Care, the League for Industrial Democracy, and the Association for the Advancement of Colored People. This conclusion was not adopted because adoption of any conclusion required the unanimous approval of the Steering Committee; and a single dissent was sufficient to defeat a proposal. But the array of strength behind this conclusion should convince even the die-hard tories in the health professions that the threat of nationalization of medical care in this country is real, is acute, and soon will be, if it is not already, sufficiently great to precipitate action by the Congress.

What then, will be the future of the voluntary prepayment plans for medical care—both commercial and non-profit? Those demanding national health insurance were generous enough to state that the voluntary plans should continue in operation after the inauguration of national health insurance. This, of course, was but a courteous gesture since it would be impossible for voluntary plans to compete with a government plan. The handicap would not be one of cost, because the voluntary plans can do the job cheaper than the government can. But the fact that the government plan would be supported at

least one-third by tax money, and that everyone would have to pay this tax, whether or not he subscribed to a voluntary plan, would dissuade the taxpayer from supporting two plans at the same time.

Since it is impossible for voluntary plans to survive if and when national compulsory health insurance comes, we are going to have one or the other type of prepayment health insurance—not both. So, the future of the voluntary plans depends entirely upon the prevention of thhe enactment of national compulsory health insurance legislation.

This cannot be prevented through political manipulation. It is my considered opinion that, if left to popular vote, this legislation might pass today.

But this disastrous legislation can be prevented if the voluntary plans meet every reasonable demand for health insurance. I specify "reasonable demand" because, as all of us know who are familiar with the problems involved, some of the demands expressed at the National Health Assembly are impossible of fulfillment at the present time, and for some years to come.

There were unanimously adopted by the Medical Care Section seven criteria for measuring the effectiveness of prepayment plans in meeting the medical care needs of the people.

The first criterion is "The extent to which a prepayment plan makes available to those it serves the whole range of scientific medicine for prevention of disease and for treatment of all types of illness or injury." To meet this criterion, voluntary plans must be in a position to offer as comprehensive a coverage as the public demands, regardless of cost. Since many people neither desire so complete a coverage, and are unwilling or unable to pay its cost, this means that plans will have to offer more than one type of contract. We must always, of course, offer a contract that is within the economic reach of the low-income groups who must bear all or part of its costs. But these large union groups are demanding a much more comprehensive service, and are willing and able to pay for it. We simply must be in a position to offer them a contract that meets their requirements, or we shall not only be forced out of business but also we shall have compulsory government health insurance as a reality instead of as a threat.

The fact that the fee schedules for the low-income group contracts are inadequate for the higher-income contracts need give no physician any concern. It is quite easy to arrange a separate fee schedule for each type of contract. For the higher-income groups, the fees should be higher, and should correspond to the fees normally charged such groups.

What can it matter to a participating physician whether the patient pays the bill from his private income, or whether the bill is paid by the medical care plans, so long as the amount paid corresponds with the fee customarily charged in that income level? Even if there is some objection to such a procedure, the alternative is to lose millions of potential patients to employee-benefit associations and medical cooperatives operating their own clinics and hospitals. I cannot stress too strongly the fact that this movement has already reached the point where the medical profession has the choice only of making a reasonable effort to meet the requirements of these large groups of consumers of medical care, or of watching the private practice of medicine in this country being rapidly strangled by either cooperative or government medicine. No other alternatives are left. All other alternatives have been lost in the 10 or 15 wasted years in which organized medicine has pursued an entirely negative course in dealing with this social problem.

The next point of the greatest importance is that these large groups will not be satisfied with anything short of uniform coverage for their members regardless of their place of

residence. They simply will not deal with 51 separate Blue Shield Plans. Already the United Mine Workers, with 400,000 members, have a 10¢ per ton levy solely for health and welfare. As we assemble here, a union with more than a million members is negotiating with a large industrial corporation for a 10¢ per hour increase in wages, to be devoted exclusively to a health and welfare program. Another union, with more than a million members, has already appointed a medical advisory council to formulate a prepaid health program for its members, to be paid for by a similar 10¢ per hour raise in pay.

Is organized medicine guiding and directing these programs? It is NOT! I happen to know some of the members of this medical advisory council of this gigantic union. I can tell you that they are openly committed to government compulsory health insurance. Let me give you the names of some of them—Fred Mott, who is directing the government medicine program in Saskatchewan; Dean Clark, who is director of H.I.P. in New York; Jack Peters, who is Secretary of the Committee of Physicians for the Improvement of Medical Care. I can tell you further that the plan for the medical care of this large union, which was proposed at the first meeting of this medical advisory council, was similar to that of the Health Insurance Plan of New York—the establishment of clinics in every center of this union population, and these clinics to be operated by salaried physicians. This Association is on record as opposing such a plan for medical care.

Why was not organized medicine approached for advice and counsel in the establishment of these huge programs for prepayment of medical care? I'll let you answer that question. But doesn't it shock you, doesn't it give you a feeling of insecurity that the leadership of these great movements, which will exert the most profound effect upon medical practice in this country—that the leadership in these movements has slipped from the grasp of organized medicine? I can tell you that it disturbs me deeply, and that I am convinced that the cause is lost unless you take prompt and effective action to regain control of medical practice in this country. I say "regain" because I am afraid you have already lost it, whether you realize it or not. And you are not going to regain it through the methods you have followed during the past 10 years.

Some three weeks ago I had a conference with one of the most powerful, if not the most powerful, labor leaders in the United States. The organization of which he is the president controls many labor unions with millions and millions of members. His closest welfare advisers made it very clear to me that they would deal with the voluntary nonprofit prepayment medical care plans only if these plans met their requirements to a reasonable degree.

The two most important principles upon which they would insist in full were uniform coverage in every area in which their members reside, and a single contract with one labor-management board regardless of the number of individual medical care plans which would be involved in providing the service. There would be no negotiation with reference to these two principles—we would have to accept them or reject them as they stand.

These gentlemen also made it clear that they were opposed to indemnity insurance and would accept this type of contract only as a temporary expedient. They are committed to the principle of service contract.

These requirements can be met, and met easily. But they cannot be met so long as our vision is limited by the boundaries of the small areas in which we live and practice medicine. The problem is one of national scope, and it cannot be solved by state and county medical societies acting independently. I can assure you that you will not even be listened to, much less dealt with, upon any such basis.

Neither one of these requirements can be met, however, without the necessary machinery at the national level of Blue Shield Plans. You know full well that it would be impossible for 51 separate Blue Shield Plans to get together around a table and agree upon a uniform contract.

Only a National Service Agency, controlled by all the participating Blue Shield Plans, can possibly meet this urgent need. My own concept of such an agency is this:

1. It would be controlled by a board of directors elected by the participating Blue Shield Plans.

2. It would underwrite medical care programs of national scope; and, in turn, would pass on to each local plan concerned the share of the business that lay within the area of that plan.

3. If any local plan desired to accept the entire risk of additional coverage offered in any contract, it would be free to do so. If, on the other hand, any local plan declined to carry the additional coverage demanded, the National Service Agency would carry the added risk, and pay the local plan for all such service rendered.

4. The National Service Agency would work only through local plans. It would write no contracts in any area covered by a plan that did not involve two or more plans, and it would offer no contract of itself except in areas not covered by any Blue Shield Plan.

5. The National Service Agency would have no control over any local plan other than to see that agreements entered into with subscribers were carried out.

6. The existing organization of Associated Medical Care Plans would not be disturbed. The National Service Agency would be an underwriting organization, and not one of control.

As a physician, who is intensely interested in the future of medicine in this country, I cannot see the slightest danger in such a project. Each local Blue Shield Plan would preserve its present degree of autonomy, and the National Agency would be one that served all the plans rather than one that controlled all the plans. And, don't forget one thing—it is either some such arrangement or be forced out of business. If we are not going to be in a position to serve these new millions of organized consumers of medical care, we had better announce that fact right now and liquidate our Blue Shield Plans.

I mentioned earlier that straw men were being set up so that they could be knocked down. Perhaps the largest of these straw men is that this is just a scheme for Blue Cross to gain control of medical practice in this country. This is not only the largest of the straw men, it is also the most fragile. I work just as closely with the Blue Cross Commission as I do with the Blue Shield Commission. I have not seen the slightest evidence of any desire—much less, intent—on the part of the Blue Cross Commission to exert even the slightest control of the practice of medicine. The cry of "No Merger" has been raised against the two Commissions. I have been instructed by the Joint Executive Committee of the two Commissions to state that merger of Blue Cross and Blue Shield has never been considered. All that has ever been seriously proposed is a federation of the two groups for the single purpose of promoting the success of both. But joining hands solely for the purpose of offering prepaid health protection in one unit is a far cry from merging the two organizations under single control.

If we get socialized medicine in this country, it will be organized medicine, and only organized medicine, that has brought this curse upon us. We, as physicians, will have only ourselves to blame. If I were among the group that wants socialized medicine in this country, I would not exhaust much energy in making a great personal effort—I would

relax and let organized medicine do the job for me. All that is necessary to bring socialized medicine to this country within a very short time is for organized medicine to pursue the same course that it has pursued for the past 10 years.

The demand for more comprehensive medical care, and for an effective means of budgeting its costs, has grown, within 10 years, from a whisper to a roar. Our people will not be denied much longer. If the medical profession does not at once assume the leadership, if it does not at once cease its double talk and double dealing with the voluntary nonprofit prepayment plans, and throw its influence squarely and honestly behind these plans, we are going to have a compulsory government health insurance in this country within three years.

I give free medicine a lease on life of three years . . . that is, unless by that time we have demonstrated that voluntary health insurance is a completely satisfactory answer to the problem. And I would emphasize further that, if we start right now, it will take at least two years to effect an organization that can do this job: We cannot afford to waste any more time in fruitless discussions that lead us nowhere. We must decide right now whether we are going to unite in this effort; and, if we are, we must cease all delaying and obstructive tactics.

Don't be lulled into a sense of security by such able studies on socialized medicine as have been made by the Brookings Institute, and the National Industrial Conference Board, and other capable agencies such as these. Of course, every thinking person is convinced that socialized medicine would be a great mistake—a costly mistake both in money and in health. But this issue will not be decided by wisdom. It will be decided entirely by emotion. Like President Coolidge's preacher, who was "agin sin," everyone is against sickness and death. Only a small minority of our people can understand the dangers of socialized medicine—all they know is that they want everyone to have good medical care, and they are not capable of choosing between the various ways in which medical care can be better distributed. Only a *fait accompli* will convince them—and so we have only a short time in which to show them an accomplished fact.

It is useless for the medical profession to undertake the education of our people to the dangers of socialized medicine. Our public relations have been so miserable in the past few years that a majority of our people suspect us of having only a selfish, personal interest in this question. I honestly believe that the medical profession does more harm than good when it attempts to decry socialized medicine—our motives are too suspect.

Don't be misled with such absurdities as the assurance that the government cannot make you practice medicine if you do not want to. You see what has happened in England. The members of the British Medical Association voted at first to have nothing to do with government medicine. The majority was heavy—80% pledging themselves to remain outside the Government plan. But, as the deadline for participation approached, British physicians by a small majority, voted to accept the government plan.

How long can you hold out in a strike against the government? How many of you could stick it a year with no income? And how many of you would stick it if you saw a minority group collecting all the gravy? You are trained in medicine. How many of you would be willing to forsake medicine and embark upon another career?

Don't let anyone fool you! If government medicine comes, 90% of you will be forced by circumstances to accept it, no matter how bitter a pill it will be for you to swallow. So, the only way to prevent this tragedy is to stop it before it arrives—there is little you can do about it after it comes. The medical profession can prevent this tragedy, but only

by positive action that will meet the reasonable demands of these large groups. Consistently negative action has brought us to this critical juncture, and has played directly into the hands of the enemies of free medicine. Time is running against us. We can not longer delay.

This convention, which is about to open, promises to be the most important in the hundred years of existence of the American Medical Association. The great work of the past hundred years can be undone overnight by unwise action during this week. I beg of you to weigh carefully the issues that will be presented. I ask you to weigh them in the light of the events of the past few weeks. I am as certain as I am that I stand here that, if this convention fails to encourage and support the expansion of the Blue Shield movement, the death knell of free medicine in this country will have been sounded.

TRENDS

IN HEALTH LEGISLATION AND ADMINISTRATION

By JOHN P. HUBBARD, M.D., *Contributing Editor*

This and subsequent descriptions of events and trends are intended to be unbiased and factual, presenting both sides of controversial matters so that conclusions may be formed from critical appraisal of things as they are. These statements do not necessarily reflect the opinion of the writer nor are they to be interpreted as official opinion of the Academy.

NOW that the national elections are in the background, we may expect to see Congressional decks being cleared for action in the 81st Congress. It is therefore in order to review the achievements of the 80th Congress in respect to health legislation.

The magnitude of the federal government's role in the development and financing of programs in the field of health can readily be appreciated by the fact that Congress appropriated approximately $165,000,000 for public health activities during the current fiscal year. Contract authorizations will raise the amount to more than $275,000,000. Besides these appropriations, the federal government assumes the total cost for many of the medical and hospital needs of the veteran population.

Among the appropriations voted by Congress for various health programs for the fiscal year commencing July 1, 1948, are the following:

Control of veneral diseases	$17,230,000
Tuberculosis control	9,291,000
General public health work	13,865,000
Control of communicable diseases	7,490,000
National Institute of Health	13,670,000
Cancer research and control	14,000,000
Hospital construction program	40,000,000
Construction of a medical research center	40,000,000
Maternal and child health services	11,000,000
Services for crippled children	7,500,000

LEGISLATION PASSED

Heart Disease Program: Congress enacted the National Heart Act. This law provides for (1) increased cardiovascular research, (2) improvement and expansion of heart disease detection and diagnostic services, (3) training of personnel both in the fields of research and matters relating to the diagnosis, prevention and treatment of heart disease. For these purposes, Congress voted an appropriation of over $3,000,000 for the current fiscal year. This program, which is to be administered by the Public Health Service, is comparable with those already operating in the fields of cancer and mental health. The law establishes the National Heart Institute and a National Advisory Heart Council consisting of 12 non-federal members, of which Dr. Paul D. White of Boston has been appointed Chairman. Included within the appropriation is an authorization for grants-in-aid to states for community heart disease programs in the amount of $500,000.

Dental Disease Program: Congress passed the National Dental Research Act to establish a program to increase research in problems of dental health and to increase training of personnel in matters related to the diagnosis, prevention, and treatment of dental diseases. For these purposes, the law authorizes an annual appropriation of $750,000.

The Act also authorizes $2,000,000 for the construction of a research and training center to be known as the National Institute for Dental Research. This Institute is to be used by the Public Health Service as a center for research and experimentation in dental diseases.

The Public Health Service is also authorized to make grants for research and training directly to universities, hospitals, other institutions or qualified individuals. Research and training projects must have the approval of an advisory council including experts in the field.

In addition to the appropriation for the National Dental Research Act, Congress voted $1,000,000 to enable the Public Health Service to establish field demonstration units for the following purposes: (1) to publicize and promote interest in the use of sodium fluoride for the prevention of dental decay in children's teeth, (2) to demonstrate the correct technics for applying the procedure and (3) to aid the training of public health personnel.

Mental Health Program: A further expansion of the national mental health program was approved. Grants-in-aid for the development and maintenance of community mental health services were increased to $3,550,000—$550,000 more than last year's appropriation. Increases were also allowed in research and training grants.

Legislation Not Passed

National Health Program: The Taft Bill (S. 545) and the Wagner-Murray-Dingle Bill (S. 1320) were the subject of very extensive hearings which have been referred to and reviewed in brief in earlier issues of this column. In the simplest terms, the Taft Bill may be described as a proposal to provide $200,000,000 a year in grants to the states for health services for those unable to pay; the Wagner-Murray-Dingle Bill proposes to establish a system of compulsory health insurance. Neither bill reached the floor of the Senate. The Senate has asked the Labor and Public Welfare Committee to submit by March, 1949, a report and recommendations on a broad national program, following a further study of existing health problems and proposed methods of meeting these problems.

The National Science Foundation: The National Science Foundation Bill (S. 526) passed in the first session and was vetoed by the President. A second bill, S. 2385, was passed by the Senate on May 5, 1948. This latter bill was designed to meet the President's objections to S. 526, the primary changes being (1) that the President, not the executive committee, would appoint the director of the Foundation and (2) that the Director would be responsible to the President instead of to the executive committee in dispensing funds. This bill passed the Senate and subsequently was reported favorably to the House by the Interstate and Foreign Commerce Committee but then died in the House.

Local Health Services: H.R. 5644, the so-called "Local Health Services Bill," proposed to provide grants to states for development and maintenance of full time local health units in all areas of the state. This bill was reported favorably to the House by the Interstate and Foreign Commerce Committee.

School Health: S. 1290 and H.R. 1980 proposed to provide about $12,000,000 a year to assist states in the establishment and maintenance of school health services for the prevention, diagnosis and treatment of physical and mental defects and conditions of school children. Neither bill was reported out of Committee.

Medical Education: Senator Thomas (Utah) introduced S. 2588 which proposed to

authorize the Public Health Service to make grants for medical education and for dental nursing and public health education. The bill included an appropriation of $18,000,000 for the first year for medical schools with additional grants to schools of nursing, schools of dentistry, and postgraduate schools of public health. Appropriations for construction of schools were also authorized.

Maternal and Child Health: S. 1714 (the current version of the Pepper Bill) provides for greatly increased grants, especially for maternal and child health programs and crippled children's services. It authorizes eventually tripling grants for maternal and child health so that every mother not covered by national health insurance would get medical, nursing and hospital care "during maternity" and every child under 18 years old would be entitled to full medical, dental and hospital care. This bill was not reported out of Committee.

Poliomyelitis: H.R. 6732, a bill to support research and training in the field of poliomyelitis was reported favorably to the House.

Expensive Drugs: A bill (S. 678) proposed to provide federal assistance to states in making expensive drugs available to needy persons. This bill was not reported out of Committee.

Department of Health, Education and Security: A bill (S. 140) was reported favorably to the Senate to create a Department of Health, Education, and Security. The primary purpose of this legislation is to elevate the existing health, education, and public welfare agencies to departmental status under a head with cabinet rank.

In this connection it should be noted that a bipartisan commission was established under the direction of former President Herbert Hoover to study and prepare plans for the reorganization of the federal government. The Commission is to submit its recommendations to Congress early next year covering not only structural changes but also recommendations on functions "in the light of their cost, their usefulness, their limitations, and their curtailment or elimination."

SPECIAL REVIEWS

JOSEPH STOKES, JR., M.D., *Editor*

VIRAL DISEASES OF THE CENTRAL NERVOUS SYSTEM. SCOPE AND LIMITATIONS OF SPECIFIC DIAGNOSTIC METHODS

By R. WALTER SCHLESINGER, M.D.
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THE AGE FACTOR IN VIRAL DISEASES OF THE CENTRAL NERVOUS SYSTEM

VIRAL diseases involving the central nervous system affect all age groups. They are, however, of special pediatric interest because the incidence of certain forms of viral meningo-encephalitis is relatively high in children. This is true not only for the neurologic manifestations in childhood diseases like epidemic parotitis or the exanthematous infections, but also for some of the epidemic forms of encephalitis.

For example, the 1941 outbreak of Western equine encephalitis in the Northwestern United States and neighboring Provinces of Canada involved about 3,000 people. Data on the age distribution of cases in North Dakota[1] and in Manitoba[2] reveal that about 5% of all patients with encephalitis were infants under one year of age. In Manitoba, 24 of 27 affected infants were less than six months old. The case rate among infants was equalled only among people over 60 years old. It is of special interest that in Manitoba, poliomyelitis was prevalent at the same time, with the highest morbidity rates in the five to 14 year age groups. Of 26 infants under one whose illness was diagnosed as poliomyelitis, only 10 were less than six months old.

These differences in age distribution between encephalitis and poliomyelitis furnish interesting epidemiologic clues. The figures for poliomyelitis suggest that a virus immunologically related to that causing the 1941 outbreak may have been widely disseminated in Manitoba at some previous time or existed endemically so that the adult population had acquired a high degree of immunity which was passively transferred to infants under six months of age.[3]

In contrast, the figures for encephalitis suggest that the population had had no previous massive experience with the virus of Western equine encephalitis. Cases covered all age groups, but the disease affected predominantly (a) those individuals who were preferentially exposed to the transmitting insects, i.e., male adults working in the fields, and (b) those who, when infected, were most likely to develop the clinically manifest disease, i.e., the very young and the very old.

This higher susceptibility of infants and of the oldest people is probably a reflection of their lesser ability to give an adequate immune response with which to overcome the infection. Sauer[4] has shown that infants two to three months of age do not react to pertussis vaccine with as high an antibody response as do older children. Similarly, vaccination of Japanese men over 60 years of age with Japanese encephalitis vaccine failed to induce antibody production although simultaneous immunization with the same lot of vaccine resulted in good antibody response in three to five-year-old children.[5]

From the Division of Infectious Diseases, The Public Health Research Institute of The City of New York, Inc. Based on a paper on "Specific Diagnostic Methods in the Viral Encephalopathies" at the Eastern Areal Meeting of the American Academy of Pediatrics, Buffalo, N.Y., May 1, 1948.

The difference between the very young and older age groups has its parallel in comparative studies on experimental animals, where it has been shown that the immune response of which an animal is capable before weaning age is not as rapid as that of older individuals. It has been possible to correlate relative degrees of immunizability with the varying degree of susceptibility to certain types of encephalitis virus.[6]

Pathogenesis and Rapid Serologic Response

Familiarity with the pattern of experimental infections with encephalitis viruses may also help in visualizing the pathogenesis of such infections in man and certain diagnostic difficulties which they present. In rabbits, for example, it can be shown[7] that after subcutaneous inoculation of Western equine encephalitis virus, there follows a brief period of viremia, comparable perhaps to the prodromal stage in man. The virus may or may not gain a foothold in the central nervous system; if it does, it may then produce an encephalitic reaction with fever which proceeds even during the period when the virus in the blood has been replaced by neutralizing antibody. The further fate of the animal is then determined largely by the relative rates of viral multiplication and of the immune response as they compete with each other, presumably within the nervous tissue.[8]

The variations in the reactions of rabbits just described illustrate particularly one factor which is of the greatest importance in the proper evaluation of diagnostic tests, i.e., the appearance of antibody very early in the acute stage and often in the absence of any sign of disease. It may be well to consider these reactions to experimental infection as typifying the group of diseases under discussion, for it is probably a justified assumption that the pathogenesis of most varieties of viral encephalopathies of man follows essentially similar patterns. Indeed, it is this similarity between diseases of such diverse etiology which makes the problem of their specific differentiation so complex.

The Diagnostic Problem in General

It is not intended in this paper to devote too much space to detailed descriptions of diagnostic laboratory technics. Critical reviews of the various procedures and adequate instructions for their use have been published by a number of authors,[9, 10] each of whom expressed his preference for one or the other technic of the neutralization test or this or that method of preparing antigens for the complement-fixation test. The existence of methodologic differences merely indicates that the field is in flux, and that new and improved methods are bound to be developed. The important question from the practical point of view is to what extent the laboratory can, under optimal conditions, fulfill the needs of the medical profession and what the clinician, pathologist, and public health officer must contribute to enable the laboratory to apply its methods intelligently.

With few exceptions, present diagnostic procedures are cumbersome and expensive, and they require all the facilities of a viral laboratory, including trained personnel. Therefore, the laboratory must set up stringent criteria for the acceptability of specimens to be tested and for cases to be investigated. The main value of diagnostic viral laboratories lies in their ability to identify the cause of a threatening epidemic, and most of the tests thus far developed have their greatest significance when used as epidemiologic tools. Prompt identification of the specific agent causing an epidemic of encephalitis is, of course, desirable because it will indicate the proper control measures to be taken. Similarly, by the speedy specific diagnosis, for example, of a case of mumps meningo-encephalitis without parotitis, further dissemination of the virus may be prevented where proper isolation measures, though indicated, had not been instituted.

But in addition, and despite the fact that specific diagnosis at this time does not provide

a guide for successful therapy, the field is new and fascinating so that each newly identified case adds to our knowledge and understanding of the problem. The magnitude of the problem results chiefly from the large number and the heterogeneity of etiologic agents involved.

Nervous tissue is a favorable medium for the growth of many viruses. Numerous viruses have been propagated in the brains of laboratory animals. Not all of them are ordinarily classified as neurotropic, since the diseases caused by them in man in nature do not usually suggest involvement of the central nervous system. Neurotropic properties shown in laboratory animals by such agents as lymphogranuloma venereum,[11] yellow fever,[12] certain strains of influenza,[13,14] dengue,[15] Rift Valley Fever,[16] Colorado tick fever,[17] viruses may, however, be related to the neurologic manifestations seen in these diseases on occasion in man.

At any rate, it has been possible in recent years to show unequivocally, i.e. by isolation of the agents, that meningitis or encephalomyelitis may be caused in man by a number of viruses ordinarily *not* classified as neurotropic, such as parotitis,[18] measles,[19] herpes,[20,21] and lymphogranuloma venereum,[22,23] viruses. Furthermore, in other common viral diseases, neurologic complications are not unusual, but isolation of their causative agents from the central nervous system (as from other organs) has failed thus far chiefly perhaps for lack of suitable experimental hosts. Indeed, it is not at all inconceivable that many of these agents may also cause meningo-encephalitis occasionally in the absence of their usual diagnostic manifestations, just as does parotitis virus in the absence of parotitis.

The same is true, after all, for infections in man with those viruses which are generally thought of as being specifically neurotropic. There, the incidence of detectable neurologic disturbances is so low in comparison with that of mild or sub-clinical infections that their definition as neurotropic is perhaps as arbitrary as would be the inclusion of parotitis virus in that group. This is true for the various forms of seasonal, arthropod-borne encephalitides, for poliomyelitis, and for lymphocytic chorio-meningitis. The wide distribution of these viruses through the "normal" population with resulting antibody formation limits the general usefulness of serologic diagnostic tests.

It is quite likely that with further improvements and with wider use of diagnostic procedures additional viruses will be incriminated as causing encephalitis or meningitis. A number of viruses have been isolated from mosquitoes in California,[24] Africa[25,26] and in South America,[27] which while immunologically distinct from those known to cause seasonal epidemic encephalitis in man, nevertheless resemble them in their behavior in experimental animals. Antibodies against them have been found in sera of presumably healthy human beings living in the areas in which the infected mosquitoes were caught. On the basis of these analogies to known encephalitis viruses it has been postulated that they may be potential causes of human encephalitis.

Another "new" virus, that of encephalomyocarditis, was isolated in 1944 by Helwig and Schmidt[28] from the organs of a gibbon and a chimpanzee which had died suddenly. The chief pathologic finding in these apes was described as interstitial myocarditis. The virus produced paralysis and myocarditis in mice. Smadel and Warren[29] have subsequently established that this virus is immunologically not related to other known viruses and that it produces a fatal disease in mice and other species. Lesions in the brains of infected mice are reported to be essentially similar to those seen in infections with other neurotropic viruses.

Within less than two years after its initial isolation from anthropoid apes, this new

virus was incriminated as a possible causative agent of "aseptic meningitis" in man by the Army Medical School group.[29] Sera obtained from cases occurring among American troops in the Philippines in 1945-6 contained specific neutralizing antibody, the titer of which rose during convalescence.

Thus, the list of viruses which may have to be considered as possible causes of meningoencephalitis is ever lengthening and the problem of their specific differentiation is becoming increasingly complicated. For practical purposes, such as may arise in connection with the setting up of a viral diagnostic laboratory, one may reduce the list to the agents enumerated in Table I. These are viruses which are known to affect the human central

TABLE I

SOME VIRUSES KNOWN TO CAUSE INFECTIONS OF HUMAN CENTRAL NERVOUS SYSTEM FOR WHICH DIAGNOSTIC TESTS ARE AVAILABLE

Seasonal arthropod-borne encephalitides	Other forms
St. Louis	Lymphocytic choriomeningitis
Western equine	Epidemic parotitis
Eastern equine	Herpes simplex
Venezuelan equine	Lymphogranuloma venereum
Japanese (B)	Rabies
Russian tick-borne	
(Louping ill?)	(Poliomyelitis)
	(Encephalomyocarditis?)

nervous system and the identification of which is readily accomplished. Poliomyelitis has been included in the list but should not be considered as being within the scope of a routine diagnostic viral laboratory. The other agents could conceivably be handled in such a laboratory by specifically trained personnel. If and when avirulent antigens for use in complement-fixation tests are made commercially available, such tests could be carried out even in routine serologic laboratories.

Almost all of the agents listed may produce in nature clinical syndromes varying in severity from mild, abortive, grippe-like fevers to severe and fatal encephalitis or myelitis. The most difficult differential diagnostic problem, by and large, is presented by the cases of intermediate severity, i.e. those of aseptic meningitis, a clinical entity which apparently may be caused by any one of the viruses listed with the possible exception of rabies virus. Thus, it is often impossible on clinical grounds alone to incriminate one and eliminate the other viruses. Yet, it is obviously not feasible to test every suspected case for all of them. All the circumstances—clinical, epidemiologic, geographic—under which a case arises should be considered and should be known to the laboratory in order to facilitate the judicious selection of agents of first importance. In addition to the usual clinical and anamnestic data, information on such factors as possible exposure to any infectious disease, vaccination, travel, living quarters with special emphasis on prevalence of insects, domestic animals, ectoparasites, rodents, etc. may furnish valuable leads. It is important to remember that all the arthropod-borne encephalitides listed in Table I are characterized by their limited geographic distribution and by their pronounced seasonal occurrence which in each instance parallels the period of highest prevalence of the insects incriminated as their transmitters in nature. This period may coincide with the poliomyelitis season, thus presenting particularly difficult differential diagnostic problems, as evidenced by the

epidemic of Western equine encephalomyelitis in Canada in 1941[2] and also by the outbreaks of Japanese encephalitis among U.S. troops on Okinawa[30] and in Korea.[31]

On the basis of all available evidence it would appear unlikely that sporadic cases of meningo-encephalitis occurring outside of the peak season of arthropod-borne encephalitis would belong in that group. Therefore, during the greater part of the year, main attention should be focused on some of the other agents listed in Table I. Here again, a thorough acquaintance of the laboratory with all the details available in each case will help in narrowing down the range of viruses which should be considered first. In the case of a child with aseptic meningitis or with encephalitis, the diagnostic efforts for routine purposes should be concentrated on tests for epidemic parotitis, lymphocytic choriomeningitis, herpes, and, perhaps, encephalomyocarditis. As regards rabies, the patient's history will as a rule, but not always, give the necessary clue. Infection of the central nervous system with the virus of lymphogranuloma venereum has been seen only in patients who presented some evidence of primary genital involvement.[22]

Specific Diagnostic Procedures

Despite the diversity of viruses capable of causing meningitis or encephalomyelitis, the specific diagnostic procedures for most of them follow essentially identical lines. The diagnosis depends either on the isolation of the agent from the patient or on the demonstration of a specific immune response or, preferably, on both.

As a rule, the presence of neutralizing or complement-fixing antibody in convalescent serum alone is not adequate proof of recent infection with the virus with which the serum reacts specifically. Most of these viruses are characterized by their endemicity in those areas where they have been found at all. As a result, a large proportion of the "normal" population has acquired serologic evidence of past infection. Therefore, a specimen of serum should be obtained as early in the course of the disease as possible. If this early specimen contains no antibody or if its titer is significantly lower than that of the convalescent serum, the presence of antibody may be considered diagnostic. These stringent criteria apply especially to the neutralizing antibody because it is maintained at high titer for many years. In certain instances, complement-fixing antibody retains a significant titer for relatively shorter periods of time; and, therefore, the demonstration of complement-fixing antibody in early convalescence is sometimes very strong circumstantial evidence of recent or current infection. Also, complement-fixing antibody may appear earlier than neutralizing antibody and when it is found during the acute or early convalescent stage in absence of neutralizing antibody it should be considered as diagnostic. On the whole, the interpretation of serologic results should not follow any rigid rules but must be adapted to the individual case. In Japan, for example, where the demonstration of neutralizing antibody in the first specimen of serum of a Japanese would have no diagnostic significance at all, a similar finding in the serum of a recently arrived nonvaccinated American with encephalitis may be considered as far more suggestive.

For the rapid diagnosis of parotitis meningo-encephalitis, the complement-fixing soluble antigen prepared by Henle, Henle, and Harris[32] may be of great value. This antigen is a fraction not sedimentable from suspensions of infected allantoic membrane at a centrifugal speed which will throw down the virus itself. The antibody reacting with it persists for a relatively short time only and has been demonstrated as early as two days after onset. When it is found early in the course of the disease in the absence of the more persistent one reacting with the sedimentable antigen, the test may be considered diagnostic even though only one serum specimen has been tested. But for this exceptional

pattern, the general rule requires that for all diagnostic tests at least two specimens must be submitted. Single specimens should not be tested and should be discarded.

A decision as to the proper time interval at which to bleed the patient for follow-up specimens will depend (a) on the urgency of obtaining the diagnosis, (b) on the particular agent or group of agents which are most likely to be involved, (c) on the availability of the patient.

An arbitrary schedule which will satisfy most needs would be: first specimen as early as possible, second specimen about two weeks later. Where speed is of the essence, changes in the antibody pattern may be shown in two sera taken only two or three days apart. On the other hand, in lymphocytic choriomeningitis, neutralizing antibody often is not demonstrable until about six weeks after onset;[33] and, because of the very low titers of complement-fixing antibody attained in this disease, the demonstration of neutralizing antibody would constitute valuable confirmatory evidence.

In general, the chances of obtaining a specific diagnosis on the basis of serologic evidence are probably greater than those of obtaining it by isolation of the virus itself. On the other hand, attempts at isolation should be encouraged because it is the most promising method of discovering new or previously unsuspected agents. Recovery of virus from the living patient depends, even more than on adequate serologic evidence, on the availability of samples taken early in the acute stage of disease.

Isolation of some of the viruses of seasonal encephalitis, of lymphocytic choriomeningitis,[33] herpes,[20] parotitis[18] and lymphogranuloma inguinale[22] from the spinal fluid has been successful in several instances. In addition, lymphocytic choriomeningitis virus[33] and, according to Japanese and Russian workers, Japanese and Russian tick-borne encephalitis viruses have been isolated from human blood. The virus of Venezuelan equine encephalitis has caused several laboratory infections, all of "grippe-like" nature and in some of these instances the virus was recovered from throat-washings or from blood.[34] These patients were presumably not infected by the natural mode of transmission, i.e. the bite of infected mosquitoes; therefore, no general conclusion should be drawn concerning the chances of virus recovery from throatwashings or blood in naturally occurring cases. In this connection it is of interest that Sulkin and Harford[35] and recently Duffy and coworkers[36] reported the recovery of rabies virus from the saliva of patients. The case described by Duffy et al. is particularly interesting because the patient's history was noncontributory and the course not entirely typical of rabies.

Most of the strains of encephalitic viruses isolated from human cases have been isolated from nervous tissue obtained at autopsy. Even failure to isolate virus from such specimens, however, does not necessarily rule out the viral nature of the infection. Repeated attempts may be necessary, and Japanese authors, on the basis of their experience with their native type of epidemic encephalitis, have recommended the wide use of "blind" passages; that is, serial brain-to-brain passages in mice without waiting for evidence of disease in the animals of the first few passages.[37] In a fatal case of herpes simplex encephalitis described by Whitman and coworkers,[21] inoculation of a pool of human cortex and cerebellum into mice failed to reveal the presence of the virus although it produced encephalitis in hamsters. But a second attempt in which a pool of cortex, medulla and pons was used also brought down all of the mice inoculated. Failure to isolate virus from brain tissue in a serologically and histologically confirmed case of Japanese encephalitis has been reported by Sabin.[30] This patient died 10 days after onset, and such negative results are reminiscent of experimental findings in laboratory animals indicating that multiplication of encephalitis virus may reach its peak well before onset of

manifest disease[8] and that the virus may be no longer demonstrable at time of death. Bodian and Cumberland[38] have studied the rate of growth and disappearance of the Lansing strain of poliomyelitis virus in the spinal cords of infected monkeys. In a given segment of the anterior horn the virus was found to be demonstrable by subinoculation into mice for only two to three days after onset of paralysis in the extremities supplied by that segment.

Because of these vicissitudes of the method, the laboratory should be supplied with portions of various parts of the central nervous system if viral isolation is to be attempted.

All tissues and other specimens to be examined for the presence of virus or, for that matter, for antibody should be obtained under aseptic precautions and should be shipped to the laboratory without delay. Where some delay is unavoidable, the specimens should be kept refrigerated. Brain tissue, spinal fluid, or serum, but not whole blood, may be frozen and packed in dry ice for shipment, but care should be taken to place the specimens in air-tight containers so as to avoid excessive exposure to CO_2. Tissue fragments may also be preserved in an autoclaved mixture of equal parts of glycerin and saline.

The isolation of parotitis virus from spinal fluid by inoculation into the amniotic cavity of eight-day-old embryonated eggs has been reported by Henle and McDougall.[18] After five days' incubation, the amniotic fluid had a slight capacity to agglutinate chicken erythrocytes; after three further amniotic passages, the hemagglutinating titer rose to 1:1024, and the amniotic fluid contained roughly 1 million/cc. infective doses.

The egg infectivity—as measured by the hemagglutinin production in the fluids of inoculated eggs—was neutralized specifically by anti-mumps rabbit serum and by human convalescent serum. Also, a complement-fixing antigen prepared from fifth passage amniotic fluid gave strong fixation in presence of convalescent but not of acute-phase sera.

Inoculation of eggs by the intra-amniotic route rather than by the technically more accessible intra-allantoic route has been recommended for the primary isolation of parotitis virus.[18] Once established in eggs—as evidenced by the high titer of hemagglutinin—the virus can be carried in eggs by the allantoic route.

For the isolation of other meningo-encephalitic viruses, the laboratory mouse is the most useful tool. All the viruses listed in Table I, with the exception of parotitis virus and most strains of poliomyelitis virus, are pathogenic and lethal for mice when injected intracranially.

If virus is present in the inoculum and multiplies in the mouse brain, it can readily be transferred by brain-to-brain passage. It can then be identified on the basis of (a) its experimental host range; (b) the characteristics of the experimental disease, including its histopathologic effect; (c) neutralization and complement-fixation tests with known standard immune sera; (d) active cross immunity tests between the new and known standard viruses.

Under favorable conditions, it should be possible to isolate and identify most of the meningo-encephalitic viruses within one week after suitable specimens are received in the laboratory. As an illustration, the experience gained in an investigation of an outbreak among an isolated contingent of American troops in Korea in the summer of 1946 may be cited. These studies were carried out in the Tokyo Laboratory of the Commission on Virus and Rickettsial Diseases, Army Epidemiological Board, and have been published in detail.[31] A brief resume follows:

The first patient died after a fulminating course of two days' duration which had been preceded by prodromal symptoms lasting two to three days. On August 28, 1946, serum taken 12 hours before death and fragments of brain and cord tissue were received at the

Tokyo Laboratory. A suspension of central nervous system tissue was inoculated into baby mice immediately upon arrival. Five days later, five of nine mice showed definite signs of encephalitis and were sacrificed. Three brains were used for the preparation of complement-fixation antigen by high speed centrifugation without further treatment. The test was set up with this and control antigens against standard immune sera on the same day. The other two brains were utilized as passage material with which a neutralization test against known immune sera was carried out immediately.

The result of the complement-fixation test was read after overnight incubation and indicated that the mouse brain antigen reacted specifically with Japanese encephalitis hyperimmune serum. A simultaneous test set up with sera obtained from the second, non-fatal case four and seven days after onset revealed the appearance on the seventh day of antibody reacting specifically with Japanese encephalitis antigen. Thus, the identity of the virus causing the outbreak was established by both isolation and serologic tests six days after the first specimen was received at the laboratory.

It was further confirmed a few days later by the outcome of the neutralization test; it is of special interest that the first patient's serum, obtained five days after onset of prodromal symptoms and 12 hours before death, contained a considerable amount of antibody neutralizing the newly isolated as well as a known strain of Japanese encephalitis virus, but no demonstrable complement-fixing antibody.

Conclusions

The scope of diagnostic procedures suitable for routine use in a viral laboratory has been discussed in relation to the general problem and the etiologic diversity of viral infections affecting the central nervous system. Diagnostic tests are available for a limited number of these diseases but their practical usefulness depends on observance of certain stringent requirements which the laboratory must impose on clinicians and pathologists who desire aid in the specific diagnosis. Among these are the choice of suitable test materials and their proper collection, storage, and shipment. It has been emphasized that all requests for diagnostic study must be accompanied by detailed clinical, laboratory, and epidemiologic data.

Since the specific diagnosis of this group of diseases does not affect therapy or outcome in the individual case, the tests available at present have their greatest practical significance as epidemiologic tools.

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Foot of 15th St.

PUBLIC HEALTH, NURSING AND MEDICAL SOCIAL WORK

LEONA BAUMGARTNER, M.D., *Contributing Editor*

INCIDENCE OF COMMUNICABLE DISEASE IN THE UNITED STATES

NUMBER OF REPORTED CASES OF 9 COMMUNICABLE DISEASES IN THE UNITED STATES DURING THE 4-WEEK PERIOD AUGUST 15–SEPTEMBER 11, 1948, THE NUMBER FOR THE CORRESPONDING PERIOD IN 1947, AND THE MEDIAN NUMBER OF CASES REPORTED FOR THE CORRESPONDING PERIOD, 1943–47

Division	Current period	1947	5-year median	Current period	1947	5-year median	Current period	1947	5-year median
	Diphtheria			Influenza[1]			Measles		
United States	579	565	871	3,235	1,947	2,233	4,239	2,761	2,761
New England	19	24	21	0	4	4	540	153	228
Middle Atlantic	41	58	58	7	9	12	889	589	589
East North Central	40	39	95	36	75	74	764	747	655
West North Central	31	43	86	28	18	23	117	251	109
South Atlantic	175	148	204	1,518	959	817	266	329	329
East South Central	122	72	152	93	56	69	87	77	50
West South Central	91	87	128	1,401	700	1,038	541	218	218
Mountain	35	38	41	117	103	118	374	126	228
Pacific	25	56	84	35	23	41	661	271	452
	Meningococcus meningitis			Poliomyelitis			Scarlet fever		
United States	168	174	299	5,758	2,370	3,436	1,357	1,549	2,746
New England	6	8	12	135	238	238	109	97	231
Middle Atlantic	24	40	65	770	423	494	217	289	408
East North Central	29	33	73	1,050	838	907	335	353	621
West North Central	19	9	21	1,017	255	360	116	195	222
South Atlantic	23	16	41	1,025	244	244	175	163	449
East South Central	27	17	29	222	58	153	147	71	162
West South Central	25	18	27	400	60	277	74	92	122
Mountain	5	14	10	165	95	166	54	100	127
Pacific	10	19	31	974	159	222	130	189	301
	Smallpox			Typhoid and paratyphoid fever			Whooping cough		
United States	2	3	10	392	485	671	3,634	12,628	8,711
New England	0	0	0	21	34	39	320	965	712
Middle Atlantic	0	0	0	38	59	94	958	2,374	2,140
East North Central	0	0	3	39	51	68	656	3,742	2,832
West North Central	0	1	1	20	30	33	197	979	543
South Atlantic	0	0	0	77	83	120	504	1,450	1,189
East South Central	1	1	1	57	66	72	123	315	307
West South Central	1	0	0	81	103	114	378	1,541	725
Mountain	0	1	0	26	25	31	257	613	475
Pacific	0	0	0	33	34	30	241	649	649

[1] New York, North Carolina, and Pennsylvania excluded; New York City and Philadelphia included.

For total United States	Cases for each week of current period				Following week
	1st	2nd	3rd	4th	
Diphtheria	121	145	144	169	
Influenza	715	904	667	949	
Measles	1,398	1,187	839	815	
Meningococcus Meningitis	43	49	43	33	
Poliomyelitis	1,308	1,411	1,512	1,527	
Scarlet fever	351	353	296	357	
Smallpox	1	0	0	1	
Typhoid and paratyphoid fever	96	107	98	91	
Whooping cough	902	906	891	935	

NEWS AND ANNOUNCEMENTS

Dr. Milton J. E. Senn has been appointed Sterling Professor of Pediatrics and Psychiatry and, Director of the Child Study Center, a new development at Yale University. The Child Study Center will have a close working relationship with the Departments of Pediatrics, Psychiatry and Public Health in the Medical School, as well as with departments in some of the other graduate schools. It is planned that physicians in training in these departments will have an opportunity to work in the Child Study Center as members of professional teams interested in growth and development, behavior and personality of the human organism. Dr. Senn goes to New Haven from New York where he was previously associated with the Department of Pediatrics of Cornell University and the New York Hospital. Dr. Senn is Chairman of the Academy's Committee on Mental Health.

* * *

Dr. Leonard Davidson has been appointed Professor and Head of the Department of Pediatrics at the University of Louisville Medical School. Dr. James W. Bruce has become Clinical Professor of Pediatrics there, also.

* * *

The following candidates were certified by the American Board of Pediatrics at Seattle, Wash., following the examination on September 10, 11, and 12, 1948:

Forrest H. Adams, M.D., Univ. of Minn. Hospital, Minneapolis 14, Minn.
Mason H. Abramson, M.D., 90 Birch St., Redwood City, Calif.
Albert T. Aldrich, M.D., 153 S. Lasky Dr., Beverly Hills, Calif.
Wesley H. Anderson, M.D., 412 First Security Bank Bldg., Ogden, Utah
Victor J. Birnberg, M.D., 6333 Wilshire Blvd., Los Angeles, 36, Calif.
George O. Boucher, M.D. 529 E. 10th St., Long Beach 13, Calif.
Mathew D. Burnett, Jr., M.D., 5101 Fannin St., Houston, Texas
Charles M. Campbell, Jr., M.D., 911 Chapala St., Santa Barbara, Calif.
Michael J. Campbell, M.D., 7943 Exchange Ave., Chicago, Ill.
Leroy O. Carlson, M.D., 717 Baker Bldg., Walla Walla, Wash.
R. Wendell Coffelt, M.D., 628 N. Glenoaks, Burbank, Calif.
John R. Connell, M.D., Children's Hospital, Denver, Colo.
Lewis T. Corum, M.D., 241 Lafayette Arcade Bldg., Tampa 6, Fla.
James O. Dowrie, M.D., 1205 24th St., Sacramento 16, Calif.
Josephine L. Earlywine, M.D., 1159 Wilmette Ave., Wilmette, Ill.
Frank L. Fletcher, M.D., 311 W. Idaho, Boise, Idaho
Thomas V. Geppert, M.D., The Henry Ford Hospital, Detroit, Mich.
Grace B. Goebel, M.D., 469 Chapman Dr., Corte Madera, Calif.
Margaret L. Goetsch, M.D., 110 W. Broadway, Glendale, Calif.
Martha H. Hale, M.D., 3403 Hall, Dallas, Texas
Herbert B. Hutt, M.D., 42 W. Midlothian Blvd., Youngstown 7, Ohio
Julius M. Kantor, M.D., 306 E. 12th St., Kansas City, Mo.
Frank McCarry, M.D., 451 Paulson Medical Bldg., Spokane, Wash.
John P. McDermott, M.D., 515 Cobb Bldg., Seattle, Wash.
Donald H. McDonald, M.D., 1442 N. Third, Abilene, Texas
John C. Montgomery, Jr., M.D., 202 Fine Arts Bldg., Bellingham, Wash.
Arthur J. Moss, M.D., 239 N. Locust St., Inglewood, Calif.
Aaron Nisenson, M.D., 6230 Wilshire Blvd., Los Angeles, Calif.
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Sam M. Powell, Jr., M.D. 1611 5th St., Corpus Christi, Texas
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Edgar M. Rector, M.D., 4212 N.E. Broadway, Portland 13, Ore.
Francis H. Redewill, Jr., M.D., 124 E. Hadley St., Whittier, Calif.
Clark M. Richardson, M.D., 829 S. Alvarado, Los Angeles 5, Calif.
Catherine F. Roberts, M.D., 1629 Selby Ave., Los Angeles 24, Calif.
Samuel M. Rosenthal, M.D., 6333 Wilshire Blvd., Los Angeles 36, Calif.

Melvin H. Schwartz, M.D., 1904 Franklin St., Oakland, Calif.
Albert J. Sheldon, M.D., 1524 N. Broadway, Santa Ana, Calif.
Ralph O. Sherberg, M.D., 508 Metropolitan Bldg., Denver 2, Colo.
Frederic E. Simpson, M.D., 234 W. Beauregard, San Angelo, Texas
Pauline G. Stitt, M.D., Territorial Dept. of Health, Honolulu, Hawaii
Philip R. Vandeman, M.D., General Delivery, Olympia, Wash.
James S. Vedder, M.D., Marshfield Clinic, Marshfield, Wis.
Elsie I. Wisczorowski, M.D., 645 Fullerton Pkwy., Chicago 14, Ill.

Examinations are now scheduled for November 17, 18 and 19, 1948 in Atlantic City; February 18, 19 and 20, 1949 in St. Louis; and April 22, 23 and 24, 1949 in Baltimore.

* * *

Forty spokesmen for the producers and consumers of health services for mothers and children met in Washington, D.C. recently to form an advisory committee to the U.S. Children's Bureau on Federal-State programs for maternal and child health and crippled children's services.

Invited by the Children's Bureau to advise it on matters of public policy affecting the promotion of better health for mothers and children, this new committee is the first in the child-health field, with representation both of nonprofessional and professional groups, to be given this broad mandate.

Members of the Committee include the following Academy fellows: Dr. Harry H. Gordon, who was elected Chairman of the Committee for three years; Dr. Harry A. Ong, representing the Academy; Dr. John P. Hubbard, representing the Academy's Improvement of Child Health Committee; and Drs. Allan M. Butler, Herbert R. Kobes; Thomas E. Shaffer; Abram L. VanHorn and James L. Wilson.

INTERNATIONAL NEWS AND REPORTS

NEWS FROM ENGLAND

ALAN MONCRIEFF, M.D., *Corresponding Editor*

The International Congress on Mental Health, which was held in London in August, included three important conferences in one. During the first week, the mornings were devoted to the International Conference on Child Psychiatry, the afternoons to the International Conference on Medical Psychotherapy, while the whole of the second week was given to sessions of the International Conference on Mental Hygiene. (The composite noun is presumably a Congress of Conferences!)

Unlike many scientific meetings, the programme was planned to cover related subjects; and, instead of a series of unconnected papers, each day took a particular aspect for its theme. The themes of the three conferences led into one another, Child Psychiatry dealing especially with "Personality development in its individual and social aspects, with special reference to aggression," Psychotherapy with the theme of guilt, and Mental Hygiene with the more general implications of Mental Health and World Citizenship.

It is encouraging that so large a Congress, including men and women from many professions and from 50 countries, could in these difficult days be got together at all, let alone fed, transported, entertained and interpreted. And yet they were. The Central Hall Westminster became a universe in miniature. The amenities of Ashburnham House, with the Abbey walls behind it, and the quiet precincts of Westminster School became the setting for an experience in communication of ideas.

The Congress began its deliberations with a study of the family and inter-personal relationships within what is still the most important unit in human society. Aggression was considered both as a driving force in self assertion, and as a destructive and hostile impulse related to frustration. A note of warning was sounded as to the effect of replacing spontaneous parental love by organised professional care, and any attempt to wear rose-coloured spectacles was sharply blocked by speakers with first-hand experience in many countries of the effects of war on children who had been orphaned and deprived of any normal home life. This served to focus attention on the need for warm parental love for every growing child, and the dual effect of its loss in producing aggressivity, or undue passivity, with its failure to build up any enduring relationship. The repercussions of such difficulties on the child's capacity to learn in school, and to grow into a contributing member of the community, linked each morning with the afternoon's theme of the rôle of therapy, using that term in its widest sense, sacred or secular, individual or group. In a most interesting series of discussions the importance of good family relationships leading to good social adaptation was repeatedly emphasized.

In going on to consider World Citizenship in the International Congress on Mental Health, the world's responsibility for its children became the focussing point for most of the discussion.

The problems posed by the war's aftermath are clear enough, and many speakers had first hand knowledge of children's camps and Homes for War Orphans in Europe. The dual responsibility of nurture and of nature in influencing the child's emotional development was stressed, particularly the former, which is so much more accessible to social influences.

The importance of the early childhood years was affirmed; whether as individuals or as members of a society, we all inevitably bear the marks of our first human relationship, that of child to parent (or to parent-substitute). Thus normal family life remains the cell around which good relationships are to be built; schools, teachers, doctors, all who work with children, and train others to do so, must acknowledge this in their work. Just as the family now moves out sooner, and further, into other social groupings, so nations form into groups, and the world shrinks. Over it all hangs the threat of immense physical destruction; upholding it is the unplumbed capacity of man who, equipped with more than just his instincts, is able to change and to adapt. The natural tendency of the child to grow right blends with the urge of mankind to "carry on the endless human adventure."

In the final summing up it was pointed out that man's mutability linked with his social organization and with his ability to form good relationships, and to experience and deal within himself with the bad relationships. The practice ground where we learn how to do this is normally the family, hence the vital importance of the earliest personal relationships within the family.

It is obvious that all this has a bearing on the work of doctors, especially paediatricians, teachers, and nurses, indeed all who come in contact with children. The value of the nursery school and its power to enhance a parent-child relationship was contrasted with the poor substitute for home too often provided by long hours of the formative years spent in day nurseries. The education of parents, the selection of teachers, and the training of doctors, especially those concerned with babies and young children were discussed. Perhaps of greatest value was the way in which this Congress related the disciplines of its many members so that doctors had to think sociologically, and teachers had to reckon with psychology in getting children to read.

During the meeting, professional groups, doctors, nurses, occupation therapists held lectures, demonstrations and films, and in a meeting where the growth and development of children was so much to the fore, it was disappointing that so few peadiatricians were present.

MILDRED CREAK

MATERNITY HOMES IN GREAT BRITAIN

The experiments with "rooming-in" in the States are being watched with considerable interest in Great Britain. Although not publicised as official policy there is little doubt that the trend here in the future for maternity homes will be largely on the lines of imitating home conditions as far as possible. Well before the World-War II, that is going back about 20 years or more, the whole of the public health and obstetric groups were strongly against what was termed "institutional midwifery." The home was the best place for a mother to have a normal confinement and two-thirds of all births took place there. Hospitals should be reserved for emergencies and difficult cases. This point of view was based on a fear of infection, both for mother and baby, and a maternal mortality rate which refused to go down despite the resources of modern hospitals and highly trained obstetric skill. Then came the sulphonamides, and puerperal infection ceased to be a menace. Next came the threat of war and something had to be done about getting mothers-to-be out of the large towns to have their babies in safety. Hence there was developed the evacuation scheme. Maternity homes were improvised for normal confinements in the reception (safe) areas by the adapting of dwelling houses, convalescent homes, hotels and boarding houses. Billets for expectant mothers were arranged in the locality. Ante-natal and post-natal hostels were provided. From 1939 to 1944 the average number of mothers dealt with each week from the London area was 250; the highest level reached was 750 to 800 a week during the flying bomb period. Up to the end of 1944 the scheme had dealt with 151,935 mothers with a maternal death rate of only 0.8 per thousand births and a neonatal death rate of only 9.6 per thousand. Not only was the emergency scheme a great success but it proved that small units for normal maternity patients could be happy homes. Of necessity accommodation was limited in certain instances to the type of small room where the baby could spend most of the day and night with the mother.

From this war-time scheme the lines of future development became clearer. Domiciliary maternity is becoming impossible because of the shortage of houses and domestic help. Hence for large towns separate maternity homes for normal patients with about 40 beds are suggested under the general management of the new Regional Hospital Boards. Abnormal patients and emergencies would go to maternity departments of the hospitals as before. The obstetric staff of the hospital would exercise a general supervision of the maternity homes. In smaller towns homes of about 20 beds are contemplated under the care of general practitioner-obstetricians with visiting specialists as required. Existing buildings may be adapted or new homes erected. In either case it is hoped that about half the accommodation may be in single rooms where the mother and baby can be together. Nursery accommodation must also be provided for noisy infants at night and for "difficult" babies in units of not more than six to eight cots. These maternity homes are to be kept as "homelike" as possible so that mothers do not feel that they are in hospital. It must be emphasized again that no official statement on such a policy has yet been made. Intelligent anticipation, based on war-time experiences and various published reports, suggests, however, that something on the lines summarized here is likely to take place.

ALAN MONCRIEFF

BOOK REVIEWS

TUBERCULOSIS: A discussion of Phthisiogenesis, Immunology, Pathologic Physiology Diagnosis, and Treatment, Francis Marion Pottenger, M.D., $12.00, 597 pages, C. V. Mosby Co., St. Louis, 1948.

This is a timely synthesis of current clinical knowledge on human tuberculosis and is particularly valuable because of the author's half-century of experience and leadership in the field. His approach to the consideration of the problem is largely immunologic and physiologic. In his discussions the author has attempted to make clinical processes stand out in their immunologic relationships to show tuberculosis in "its dual aspect of a metastasizing-destructive as well as a localizing-healing disease."

The student of childhood tuberculosis will find here a valuable source of information as well as much mental stimulation concerning solved and unsolved problems in this disorder. The greater part of the book, however, deals with the disease as it appears in the adult subject. Particularly recommended are the first six chapters which deal with the subject of phthisiogenesis. Chapter One is introductory. Chapter Two is a discussion of the bacilli of infection—the number required to set up a focus, the portal of entry, including the two schools of aerogenous infection (dust or droplets as the chief source) and the ingestion theory. Chapter Three is devoted to the primary complex—its frequency, location, diagnosis, aftercourse and healing. The next three chapters are concerned with reinfection. The author repeatedly emphasizes the importance of the immunity that is conferred by the primary infection and states that bacillemia is a common occurrence after the primary infection has taken place. He includes a rather detailed discussion of the factors favoring the apical involvement in reinfection. The old question of the relative importance of endogenous and exogenous sources of bacilli of reinfection is considered and the author clearly favors the former. Chapter Eight, which is 32 pages in length, is a consideration of the specific problem of tuberculosis in childhood.

Ample illustrations of clinical types of the disease by case reports and reproductions of roentgenograms are included. Here not much is added to the usual sources of information concerning tuberculosis in this age group. In one brief chapter immunization against tuberculosis is discussed. In view of the current revival of interest in this important aspect it would seem that somewhat greater detail would have been appropriate. The remainder of the book deals largely with phases of the subject of interest to those in the field of adult tuberculosis.

It should be added that some of the ideas expressed by Dr. Pottenger are not entirely in accord with those of some current writers on the subject of childhood tuberculosis. Perhaps rather than a disagreement it is a matter of placing emphasis on certain aspects of the disease in childhood. This volume is a valuable contribution and it is recommended to all those who are interested in the problem of tuberculosis.

ERLE E. WILKINSON

A PSYCHOLOGY OF GROWTH, Bert I. Beverly, M.D., $2.50, 235 pages, Whittlesey House, McGraw-Hill Book Co., Inc., New York—London, 1947.

This book is based on a series of lectures on psychology which the author has given to student nurses. The publisher recommends it for professional groups in child care and also for parents. It should be a good introductory text for nurses, physicians, teachers and other professionals. Part of it would be helpful to parents too. But other parts, which emphatically and no doubt justifiably blame parents for many behavior problems, would create only guilt and further confusion in the parents to whom it applied.

The author discusses such topics as normal emotional development, feeding, toilet training, companionship, discipline, intelligence, mental testing, schooling, fears, enuresis, stuttering, stealing, hospitalization, operations, adolescence, delinquency. The emphasis is on respecting the child's own developmental pattern, providing him with love and acceptance, avoiding excessive expectations and criticism. The language is non-technical and easily understood, and there are many short illustrative case histories.

A psychiatrist might complain that the dynamics of emotional disturbances as given here are too simple. A teacher might protest that the good nursery school does more for children than "leave them alone to play as they like, work out their own standards of conduct, and settle their own differences." Even the pediatrician would question the assertion that "most children train themselves for bowel movements during the day—and remain dry between twelve and eighteen months." Such faults are probably in large part due to the effort to cover a large amount of ground in a short book. But the beginning student in child care will find the brevity and simplicity welcome—and not seriously misleading if he does not take it as the final word.

BENJAMIN SPOCK

TEACHING PSYCHOTHERAPEUTIC MEDICINE, Helen Leland Witmer, Editor. $3.75, 449 pages. The Commonwealth Fund, New York, N.Y., 1947.

This book is a striking account of how 25 general practitioners, under the skilled direction of a small group of psychiatrists, came to see, understand and handle some of the basic emotional problems that belong to all human beings sick or well. Few books follow so faithfully and honestly each step in the development of insight on the part of the physician.

It has unique value for the physician unable to take such a refresher course. It answers the questions he would ask. It translates into clear practical terms the often-times baffling problem of treating a patient as a "total human being." For the pediatrician in particular there is an invaluable discussion of the normal personality growth and development of the child, the proper understanding of which is the key to a more penetrating appreciation of the problems of the adult as well as the child.

This book makes obvious that the practice of psychotherapeutic medicine rightfully belongs in the hands of the general practitioner as well as specialists in fields other than psychiatry. To make use of the principles so plainly outlined would mean not only better care of the patient, but greater personal satisfaction to the physician in charge of that patient.

MARY E. MERCER

U. S. CHILDREN'S BUREAU PUBLICATIONS, Washington 25, D.C.

No. 8, Breast Feeding, 1947. $0.10.

No. 13, When You Adopt a Child, 1947. $0.10.

No. 1, So You're Expecting a Baby, 1947. $0.10.

Booklets for parents. Of interest to pediatricians and general practitioners too. May be useful for distribution by doctors. Brief well written, safe and sound advice.

No. 270, The Road to Good Nutrition, Lydia J. Roberts, $0.15, 51 pages, 1947.

Second revision, in light of recent advances in scientific knowledge.

No. 319, Educational and Employment Opportunities for Youth, 30 pages.

A report and recommendation of the Interagency Committee on Youth Employment and Education to the Director of War Mobilization and Reconversion, a Committee composed of representatives of Federal agencies whose program particularly concerns youth.

No. 320, Helping Children in Trouble, 17 pages.

A further study of a special phase of the St. Paul Experiment in child welfare. Four case histories with a discussion of getting help to (1) the right child (2) at the right time (3) from the right place and (4) for the right thing. A psychology of delinquents with remedies proposed.

No. 321, A Community Plans for Its Children, 54 pages.

This is the final Report of the Newport News, Va., Project, which draws conclusions from the experience of observing a community in the process of organizing itself to work on the prevention of juvenile delinquency which is basic for dealing with a variety of social problems.

LETTERS TO THE EDITOR

Re: Anaerobic Metabolism in the Newborn Infant. I. On the Resistance of the Fetus and Newborn to Oxygen Lack, James L. Wilson, M.D., et al, PEDIATRICS 1:581, 1948.

July 6, 1948

To the Editors:

In their recent article Drs. Wilson et al have undertaken a reinvestigation of the problem of the acid-base balance of the premature infant. The authors conclude from a review of the literature and their own findings that a "paradox" exists. On the one hand, the effect of oxygen on the respiration would indicate a condition of inadequate pulmonary respiration, while, on the other, the data on plasma CO_2 and pH, "interpreted in the usual way," would point to overventilation. They reject as improbable the thought that a difference might exist between oxygen and CO_2 in their rate of diffusion through the alveolar membrane. Instead, they propose that an incomplete metabolism might lead to a lower production of CO_2.

The purpose of this letter is to direct attention to studies by M. Krogh and A. Krogh (J. Physiol. **49**:271; **52**:391) in which a great difference in the diffusibility of the two gases through biologic membranes was demonstrated, with the CO_2 diffusing at a 20-30 fold rate compared with oxygen. The 50 fold greater solubility of CO_2, compared with O_2 and H_2O, is responsible for this phenomenon. Accepting the difference in diffusibility, a reasonable explanation of the apparent paradox offers itself. The relatively thick interstitial alveolar tissue of premature infants, by interposing a longer pathway for the diffusion of oxygen, would interfere with the oxygenation of the blood, while still permitting the more rapidly diffusing CO_2 to escape. The condition of anoxemia, by giving rise to hyperventilation, would secondarily cause reduction of the alveolar CO_2 tension below normal. The process of hyperventilation would tend to produce a respiratory alkalosis which may be compensated by renal activity. The anoxemia may lead to accumulation of organic acids, among which only lactic acid has quantitative importance.

In summary, then, a condition of compensated respiratory alkalosis, possibly combined with some anoxic acidosis, would exist in the premature infant. All data presented by the authors fit satisfactorily with such an explanation. A similar pattern has been found and traced in detail from man at high altitudes. It is found in lobar pneumonia and in other conditions of progressive interference with air exchange.

I should also like to comment on the hypothesis of the authors that a decreased CO_2 production could account for differences in the CO_2 content of the blood or the alveolar tension of CO_2. It may suffice to point out that in man from infancy on, despite a 20-fold increase in body weight, the CO_2-pH relationship remains constant. The same constancy is found throughout the range of all mammalian species over a more than 1000-fold span of body weight. Human pathology offers a host of other examples. Two may be cited: (1) In diabetic acidosis a low CO_2 content and tension may co-exist with an increased rate of metabolism. (2) Wide variations of respiratory quotient may exist entirely independently of the CO_2-pH relationship of the blood. In short, the CO_2-pH relationships are determined by the pulmonary and renal regulatory mechanisms and not by the total metabolism of the body.

One other point may be mentioned. The authors consistently refer to hyperventilation only as related to acidosis. It is well known that hyperventilation can arise from central stimulation, whether it be voluntary or caused by oxygen lack or a variety of other stimuli of the respiratory center.

Sincerely yours,

(signed) SAMUEL RAPOPORT, M.D.

AUTHOR'S REPLY

The points raised by Dr. Rapoport have been of great interest to us and gave us great concern in our own work and its later interpretation.

For clarity we attempt to summarize: We have pointed out that premature babies have a low plasma carbon dioxide content and an increased pH compared mith what is accepted as normal and probably have a partial anoxia due to inadequate ventilation, although this last is based upon

circumstantial evidence. (Actual studies of hemoglobin saturation are now in progress in our laboratory.) Since a low plasma carbon dioxide content usually results from hyperpnea a simultaneous inadequate pulmonary ventilation constitutes this paradox in light of usual experience. I believe our critic accepts this. The difference of opinion lies only in the interpretation offered and we believe no crucial evidence exists on which the argument can be decisively settled.

Dr. Rapoport accepts an explanation that we minimize in our discussion—that is, that the premature lung with its excessive interstitial tissues offers a greater barrier to diffusion of oxygen than to carbon dioxide, and that the greater speed of diffusion of the carbon dioxide molecule allows its excretion to be excessive while at the same time oxygen absorption is less than normal. The fact that carbon dioxide molecule diffuses through biologic membranes faster than oxygen is thoroughly established. It is not necessarily true that this difference exists for the transportation of these two gases between the alveoli and the pharynx. We cannot prove that Dr. Rapoport's choice of an explanation of the phenomena we have described is the wrong one. We can point out, however, that similar irregular respirations, corrected by the administration of oxygen, are seen in full term babies who presumably do not have the same architectural abnormality in the lungs as do premature babies. We encounter similar, though by no means exactly similar, circumstances in many clinical situations in babies, such as in so-called "capillary bronchitis" where exudate or transudate so interferes with the free passage of gases as to cause marked dyspnea. Here we see partial anoxia but an elevated plasma carbon dioxide level causing a retention carbonic acid acidosis indicating in a crude way that carbon dioxide excretion still seems to parallel the absorption of oxygen. We can only reiterate that we doubt that the difference in diffusability of oxygen and carbon dioxide in the premature lungs, as distinct from mature lungs, is great enough to be an adequate explanation, but the matter is still open to proof. The question could be settled decisively if only we had some means of determining very accurately alveolar oxygen and carbon dioxide levels at the same time as arterial determinations are done. We spent much time in wishful thinking about the advantages that such technics would offer us, but unfortunately they are not available.

Another answer which would help settle the argument is that to the question of the existence or nonexistence of the hyperpnea in these babies. Dr. Rapoport seems to reason that hyperpnea exists in the healthy premature infant, and that the hyperpnea results in a respiratory alkalosis, this compensated by "renal activity." The tendency to compensation would, of course, have to be excessive since we, as well as others, have shown that a low pH in an uncompensated acidosis actually exists. Hyperpnea implies excessive respiration and of course is a relative matter. We learn how to recognize it in ordinary patients but we do not know just what we are seeing in premature babies. However, continuous quantitative records of their respiration makes it clear that they do not have the type of continuous deep respiration which we are accustomed to observing in individuals who abnormally lower their blood carbon dioxide, either with central stimulus or as a compensation for the collection of acid products. Premature babies almost invariably breathe either with grossly irregular respirations or with the symmetrical irregularities that we have described, with long periods of apnea. These long periods of apnea certainly do not suggest the usual response to acidosis by hyperpnea.

The plasma carbon dioxide level seems obviously determined by a balance between carbon dioxide production and its excretion. A low plasma carbon dioxide content in apneic newborn has been reported by Yandell Henderson, and by Eastman. This can only be the result of failure of production of carbon dioxide. We do not understand Dr. Rapoport's statement that "from infancy on, despite a 20 fold increase in body weight, the carbon dioxide-pH relationship remains constant." The constant ratio is not between pH and carbon dioxide but between pH and the ratio carbonic acid/bicarbonate. The relationship between pH and the carbonic acid/bicarbonate ratio is expressed by the classical Henderson-Hasselbach equation—used in our calculation of the values for dissolved carbonic acid from the determined values of plasma and total bicarbonate level.

Finally, we must again point out that the existence of a type of partial anaerobic metabolism leading to an endpoint other than carbon dioxide has been pretty thoroughly established in young animals by the beautiful work of Himwich and Fazekas through experiments which are not possible in the human young.